

Report Appendices of the Peer Consultation Meeting on p-Dioxane

Volume II

Voluntary Children's Chemical Evaluation Program (VCCEP)

**May 1-2, 2007
Erlanger, Kentucky**

**Peer Consultation Organized by
Toxicology Excellence for Risk Assessment
(<http://www.tera.org/peer/>)**

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Appendix A

Voluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultations on P-Dioxane

May 1-2, 2007

List of Attendees

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VCCEP Peer Consultation for p-Dioxane
Northern Kentucky University, METS Center
May 1-2, 2007
List of Attendees

*Dr. Katherine Anitole
U.S. Environmental Agency

Dr. Dan Briggs
Toxicology Excellence for Risk Assessment (*TERA*)

*Ms. Christina Cinalli
U.S. Environmental Agency

Dr. Michael L. Gargas
The Sapphire Group, Inc.

Mr. Richard P. Hubner
The Sapphire Group, Inc.

Mr. Oliver Kroner
Toxicology Excellence for Risk Assessment (*TERA*)

*Dr. Ramez Labib

Ms. Patricia Nance
Toxicology Excellence for Risk Assessment (*TERA*)

Mr. Alan Olson
Ferro Corporation

Ms. Jacqueline Patterson
Toxicology Excellence for Risk Assessment (*TERA*)

*Ms. Lori Peterson
Kao Brands Company

*Dr. Stephen D. Soileau
Kimberly-Clark

Mr. Richard B. Stalzer
Ferro Corporation

*Web cast Participant

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Appendix B

Voluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultations on P-Dioxane May 1-2, 2007

Agenda, Overview, Panel Charge, Panelist Biographical Sketches and Conflict of Interest/Bias Disclosures, and Presenter Biographical Sketches

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Agenda
VCCEP Peer Consultation for p-Dioxane
Northern Kentucky University, METS Center
May 1-2, 2007

Tuesday, May 1, 2007

8:00 Registration and Check In

8:30 Meeting Convenes*

Welcome: Jacqueline Patterson, *TERA*

Introductions and Disclosures, Panel

Meeting Process: Michael Dourson, *TERA*, Panel Chair

9:00 Sponsor Introduction

Presenter: Alan Olson, Ferro Corporation

Sponsor Presentation on Hazard Assessment

Presenters: Michael Gargas and Richard Hubner, The Sapphire Group, Inc.

Clarifying Questions from Panel

Public Comments on Hazard Assessment

Clarifying Questions from Panel and Sponsors

Panel Discussion of Hazard Assessment

Discussion of Panel Charge Questions Regarding Hazard Assessment

12:15 Lunch

1:15 Sponsor Presentation on Exposure Assessment

Presenters: Rick Stalzer, Ferro Corporation and

Richard Hubner, The Sapphire Group, Inc.

Clarifying Questions from Panel

Public Comments on Exposure Assessment

Clarifying Questions from Panel and Sponsors

Panel Discussion of Exposure Assessment

Discussion of Panel Charge Questions Regarding Exposure Assessment

5:00 Adjourn

* Chair will call mid morning and mid afternoon breaks at convenient times

Wednesday, May 2, 2007

8:00 Registration

8:30 Meeting Re-convenes*

Sponsor Presentation on Risk Characterization

Presenters: Michael Gargas and Richard Hubner, The Sapphire Group, Inc.
Clarifying Questions from Panel

Public Comments on Risk Characterization

Clarifying Questions from Panel and Sponsors

Panel Discussion on Risk Characterization

Discussion of Panel Charge Questions Regarding Risk Characterization

12:15 Lunch

1:15 Sponsor Presentation on Data Needs

Presenters: Richard Hubner and Michael Gargas, The Sapphire Group, Inc.
Clarifying Questions from Panel

Public Comments on Data Needs

Clarifying Questions from Panel and Sponsors

Panel Discussion on Data Needs

Discussion of Panel Charge Questions Regarding Data Needs

4:30 Closing Remarks and Evaluation of Meeting

5:00 Adjourn

* Chair will call mid morning and mid afternoon breaks at convenient times

Overview of the Peer Consultation Process

This document provides background information on the VCCEP pilot program and the peer consultation. It is presented in two parts: General Background on VCCEP and Overview of How *TERA* Organizes and Conducts VCCEP Peer Consultation Meetings. The expectations for panelists and their responsibilities before, during, and after the panel meeting also are briefly discussed. Please contact Dr. Dan Briggs at <mailto:briggs@tera.org> if you have questions or desire additional information.

General Background on VCCEP

In the December 26, 2000 Federal Register, <http://www.epa.gov/fedrgstr/EPA-TOX/2000/December/Day-26/t32767.htm> EPA announced the Voluntary Children's Chemical Evaluation Program (VCCEP) pilot program. This program is intended to provide data to enable the public to understand the potential health risks to children associated with certain chemical exposures. The key questions of the program are whether the existing data on a given chemical are sufficient to adequately characterize the potential hazards, exposures, and risks to children and prospective parents, and, if not, what additional data are necessary.

The VCCEP pilot program uses a tiered testing approach. For toxicity (health effects) data, specific types of studies have been assigned to one of three tiers. For exposure data, the types of studies required are less specific, but the depth of exposure information increases with each tier.

EPA asked companies which manufacture and/or import 23 chemicals found in human tissues and the environment to volunteer to sponsor an evaluation of their chemicals in a pilot of the VCCEP. Sponsorship requires the companies to collect or develop health effects and exposure information on their chemicals and then to integrate that information in a risk assessment and a data needs assessment. If data needs are identified through this process, the sponsor will choose whether or not to volunteer for any additional data generation or testing and whether to provide additional assessments. Thirty-five companies and ten consortia responded and volunteered to sponsor 20 chemicals in Tier 1.

TERA was awarded a Cooperative Agreement by EPA to design, develop, and manage a peer consultation process that would serve as a public scientific forum. One of the activities undertaken by *TERA* under this agreement is the VCCEP pilot program. *TERA*'s primary role in this program is to ensure it is a rigorous, science-based process for reviewing VCCEP assessments. Stakeholders should recognize the process as impartial and of significant technical merit and value. *TERA*'s role in managing the peer consultation is undertaken primarily at the request of and for the benefit of non-federal VCCEP stakeholders, particularly the sponsors of VCCEP chemicals.

Overview of How *TERA* Organizes and Conducts VCCEP Peer Consultation Meetings

TERA is an independent non-profit organization with a mission to protect public health through the best use of toxicity and exposure information in the development of human health risk assessments. For the VCCEP pilot program, *TERA*'s responsibilities include identifying and recruiting scientists with relevant expertise to comprise a peer consultation panel, identifying and managing conflict of interest and bias issues of the panel candidates, organizing and conducting the peer consultation panel meetings, and drafting and finalizing the meeting reports.

The panel meeting provides a science-based peer consultation on the data needs for the chemical, utilizing not only the assessment submitted by the sponsor, but also the expertise and knowledge of the panel. Members of the peer consultation panels are selected by *TERA* based on their expertise in scientific disciplines relevant to the chemicals, test methodologies, and risk assessment issues that will be discussed. Nominations for panel members are welcomed from all interested parties. *TERA* selects the panel members from among those nominated and also from among other qualified experts whom *TERA* independently identifies.

Each panel candidate discloses information regarding potential conflicts of interest and biases. *TERA* evaluates these disclosures in selecting the panel members following procedures in accordance with the U.S. Office of Management and Budget, the National Academy of Sciences, and the U.S. EPA. These procedures are described in more detail at <http://www.tera.org/peer/COI.html>.

Panel members also are selected to bring a wide range of views and perspectives to the peer consultations, reflecting the interest in VCCEP by a wide range of stakeholders. The panel does not attempt to reach consensus positions; rather, the individual opinions of each of the members are noted.

Members of the public are invited to attend the peer consultation meetings, and they are invited to provide brief oral and written technical comments on the assessment document for the panel's consideration. Recent panel meetings have been made available to pre-registered, off-site observers via real-time web casts.

TERA reviews the sponsor's VCCEP chemical assessment document and develops a panel charge to guide the panel in its discussions during the meeting. The panel charge focuses the meeting discussions by presenting specific items for the panel to address. General questions regarding completeness and interpretation of data are included, as well as more specific questions relevant to the hazard, exposure, or risk characterization of the specific VCCEP chemical being evaluated. The charge includes questions regarding data gaps and data needs and asks panelists to identify data needs and their rationale for them.

TERA is responsible for all meeting preparations including travel and logistics, announcements, distribution of the review materials, and assisting the panel. VCCEP peer consultation meetings generally follow a standard *TERA* process, beginning with a close examination of the sponsor's report and supporting documentation by the panel prior to the meeting.

At the beginning of the meeting, panelist disclosures regarding potential conflict of interest and bias issues are presented and discussed. *TERA* believes transparency in these matters is important and therefore discusses these openly at the meeting, allowing panel members to question one another. These disclosures are also part of the public record through inclusion in the meeting report. The Chair then discusses the ground rules for the meeting. Ground rules generally include the following items:

- Chair will call upon panel members in turn and will interrupt discussion if he thinks the topic is drifting. He will not call upon observers. Observers can talk to the Chair or to *TERA* staff during a break in the meeting if they wish to schedule a time to comment.
- If a panelist states a part of the assessment unacceptable, he or she will be asked to explicitly state what additional work would be needed to make it acceptable. The Chair may ask the panelist to work with the sponsor to resolve the issues during the breaks.
- Panel members will have provided pre-meeting comments before the meeting. These comments are informal and not part of the meeting record. They are initial thoughts that were shared with

the sponsor and other panel members to help identify issues and new data. Panel members must raise items in their pre-meeting comments during the meeting in order for them to be included in the meeting record.

The meeting discussions are limited to panel members. One or two authors or sponsor representatives sit at the table to answer panel questions. These representatives are allowed to ask the panel members clarifying questions as needed. In order to avoid the appearance of undue influence on the panel, all parties are asked to refrain from discussing issues related to this review with panel members prior to the meeting or during the breaks unless a panel member initiates the discussion. Panel members are asked to summarize any substantive conversations for the rest of the panel and audience when the meeting reconvenes after the break.

The discussion period begins with the authors or sponsors making short presentations summarizing their report and possibly also addressing issues raised by the panelists in their pre-meeting comments. These presentations highlight salient issues and give the panel the opportunity to ask clarifying questions. The Chair then leads the panel in discussions, using the items in the panel charge. Individual panelists will be asked to share their opinions and defend them with scientific data and analysis.

TERA scientists take notes of the meeting discussions and prepare a draft meeting report summarizing the panelists' discussions, conclusions and recommendations. This report is not a transcript of the meeting but a summary of the key discussions and issues. Panel members are listed, but their individual comments are not attributed to them by name. The draft report is reviewed by the panel. The sponsors also are allowed to review the draft report, but they must limit their comments to matters of clarity and completeness regarding their presentations and their remarks made at the meeting. The meeting report includes copies of the sponsor presentation slides, a list of attendees, panel biographical sketches and COI/bias disclosures, and public comments. When finalized, the meeting reports are made available to the public on *TERA*'s Peer Review and Consultation website (<http://www.tera.org/peer/welcome.htm>).

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VCCEP Peer Consultation for p-Dioxane

Panel Charge

Introduction

The primary objective of this Peer Consultation Panel is to discuss whether the potential hazards, exposures, and risks for children have been adequately characterized for p-dioxane, based on the information contained in assessment documents submitted by the sponsors and on other available information. If the potential hazards, exposures, and risks cannot be adequately characterized, then data needs should be identified. The focus of the panel meeting is not on reviewing the adequacy of the report *per se*, rather a review of the adequacy of the available data. The panelists use the document and its references as a source of information, along with their own personal information and knowledge. The panel's goal is not to reach consensus positions on any issues or conclusions. Panelists who believe the chemical has not been adequately characterized will be asked to identify what additional information is needed and why they believe it is necessary. All the panelists will be encouraged to discuss and debate each other's suggestions and comments, providing scientific rationales for their points of view. TERA will compile a summary of the panel discussions in a meeting report that will be sent to the sponsor and made available to the public.

TERA has prepared this charge to help the panel discuss the sponsor's p-dioxane submission and address whether the chemical has been adequately characterized. The topics are consistent with the directions for VCCEP submissions given in the December 26, 2000, Federal Register: <http://www.epa.gov/chemrtk/vccep/>.

Panelists should keep in mind the following directives from the Federal Register regarding any recommendations for additional testing: (1) if specific toxicity studies are indicated, they should be chosen from the next tier of studies within the overall framework. They should allow flexibility to pursue either additional toxicity testing and/or exposure evaluation, allowing sponsors to select the option which will most quickly, directly, and cost-effectively reduce uncertainty and allow the creation of a risk assessment; (2) EPA is committed to avoiding duplicative testing, and to reducing, refining, and replacing animal testing when valid alternatives exist; (3) if relevant alternative test methods become validated, EPA will consider their immediate implementation in the program; (4) EPA encourages sponsors to combine tests where possible to conserve resources and reduce the number of animals required for testing; and (5) the Tier 2 and Tier 3 testing will be limited to chemicals for which there is a clear testing need.

Hazard Assessment

1. Discuss whether the available information on acute and chronic toxicity, mode of action, and ADME (absorption, distribution, metabolism, and elimination) is adequate to identify and assess all potential hazards.
2. Discuss whether the hazard data are sufficient to identify potential risk for each of these target populations:
 - prospective parents
 - embryo and fetus
 - nursing infants
 - post-nursing children through adolescence to the age of sexual maturation.
3. Discuss whether the data presented adequately support the report's conclusion that p-dioxane is non-genotoxic and requires high, prolonged dosing to produce the tumors observed in animal studies. Also, discuss whether the available data support the report's conclusion that the tumors observed in animal studies occurred only in the presence of cytotoxicity.
4. Discuss any other significant issues related to the p-dioxane hazard assessment.

Exposure Assessment

5. Discuss whether the fate of p-dioxane is adequately understood, both in the environment and within the human body.
6. Are the potential sources of p-dioxane exposure adequately identified? Are there other sources that should have been considered?
7. Discuss whether the available data are adequate regarding the following exposure aspects: frequency, duration, and intensity.
8. Discuss whether the data, age groupings, parameters, assumptions, and scenarios used in the exposure assessment were appropriate to characterize risk to children. Should other data or scenarios have been evaluated, or should different assumptions have been used?
9. Is the combination of monitoring data from the 1980s plus the use of probabilistic modeling sufficient to estimate the current exposures to p-dioxane?
10. Discuss whether the estimates of exposure were modeled and calculated correctly.
11. Discuss any other significant issues related to the p-dioxane exposure assessment.

Risk Characterization

12. For non-cancer endpoints: Although the U.S. EPA has not developed reference values for p-dioxane, other regulatory bodies have. The report presents these existing values and then derives values of its own. Discuss whether the available data support the proposed reference doses presented in the report.
13. For cancer endpoints: Discuss whether the risk characterization approach, which used cancer potency factors that assumed a no-threshold response and results from physiologically based pharmacokinetic modeling, is appropriate and adequate for the human target populations (prospective parents, embryo and fetus, nursing infants, post-nursing children).
14. Discuss whether the risk characterization adequately characterized the risk for each of these target populations:
 - prospective parents
 - embryo and fetus
 - nursing infant
 - post-nursing children through adolescence to the age of sexual maturation.
15. Discuss any other significant issues related to the p-dioxane risk characterization.

Data Needs

16. Identify any additional hazard information that is needed to be able to adequately characterize risks to children and discuss why it is necessary. Differentiate between *data gaps*¹ and *data needs*². Focus on those studies indicated for the next VCCEP tier.
17. Identify any additional exposure data or analyses that are needed to be able to adequately characterize risks to children and discuss why this information is necessary for the next VCCEP tier. Differentiate between *data gaps* and *data needs*.

¹ In the context of the VCCEP pilot program, *data gaps* are defined as areas that could benefit from additional data, additional analyses, or clearer presentation.

² In the context of the VCCEP pilot program, *data needs* are defined as data gaps requiring additional work before the potential risk to children can be adequately characterized. Not all data gaps will be considered data needs. The panelists may consider the risk characterization results when determining whether a data gap is a data need.

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VCCEP Peer Consultation for p-Dioxane

Panelist Biographical Sketches and Conflict of Interest Disclosures Presenter Biosketches

Background

Following NAS guidance, *TERA* creates panels that have a balance of scientific viewpoints on the issues to be discussed. As a result, *TERA*'s panels have a broad and diverse range of knowledge, experience, and perspective, including diversity of scientific expertise and opinion. In addition, *TERA* creates panels with multiple organizational perspectives (e.g., academic, consulting, environmental, government, and industrial/commercial). However, panel members serve as *individuals*, representing their own personal scientific opinions. They do not serve as representatives of their companies, agencies, funding organizations, or other entities with which they are associated. Their opinions should not be construed to represent the opinions of their employers or those with whom they are affiliated.

TERA is conducting this VCCEP p-Dioxane Peer Consultation under its Peer Consultation Program. This program is principally funded by a Cooperative Agreement with the U.S. EPA, the purpose of which is to design, develop, and manage a Peer Consultation process that will serve as a public scientific forum. *TERA*'s role in managing the peer consultation is undertaken primarily at the request of and for the benefit of non-federal stakeholders, particularly the sponsors of VCCEP chemicals.

TERA has performed work for organizations associated with VCCEP, both in the past and at the present time. These include the U.S. EPA, the American Chemistry Council, and some companies that are sponsors of VCCEP chemicals. *TERA* has conducted assessments and analyses for a number of chemicals included in the VCCEP pilot program in the past (i.e., acetone, decabromodiphenyl ether, methyl ethyl ketone, toluene, and xylenes) and currently is doing work on trichloroethylene. This work has been done for a variety of public and private sponsors, but none of it is directly related to the VCCEP assessments. *TERA* has not conducted work for the VCCEP p-dioxane sponsor (Ferro Corporation, Inc.) or done any other work involving p-dioxane.

The purpose of this VCCEP p-Dioxane Peer Consultation is to gather the scientific opinions of a range of experts with relevant knowledge and experience, including those who may be affiliated with organizations or companies with an interest in the outcome. All panelists were selected by *TERA* based upon their expertise and qualifications. They are employed by many types of organizations. *TERA* strived to create a balance of expertise and affiliations for this consultation meeting; however, *individual panel members represent their own expertise and views*, not those of their employer, of any group who may have nominated them, or any group with whom they may be associated. This panel is a distinguished group with many years experience in a wide range of disciplines.

An essential part of panel selection is the identification and disclosure of conflicts of interest and biases. Prior to selecting the core and *ad hoc* panelists, *TERA* requested each panel member to complete a questionnaire to determine whether their activities, financial holdings, or affiliations could pose a real or perceived conflict of interest or bias. The completed questionnaires were reviewed by *TERA* staff and discussed further with panel candidates as needed. (See <http://www.tera.org/peer/COI.html> for *TERA*'s conflict of interest and bias policy and procedures for panelist selection). *TERA* has determined, and each panel member has certified, that he or she has no conflicts of interest and is able to objectively participate in this peer consultation.

VCCEP p-Dioxane Peer Consultation Meeting

Panelist Biosketches and Disclosure Statements

Dr. Michael Dourson

Dr. Dourson directs Toxicology Excellence for Risk Assessment (*TERA*), a nonprofit corporation dedicated to the best use of toxicity data for estimating risk assessment values. *TERA*'s projects include the development of complex risk assessments, such as soluble nickel salts; research into improvements of risk methods, such as differential sensitivity of children and adults to chemical toxicity, organizing peer review and consultation meetings for risk assessment topics and documents; and education and outreach on risk assessment values through lectures and data bases, including the International Toxicity Estimates for Risk (*ITER*).

Before founding *TERA* in 1996, Dr. Dourson held leadership roles in the U.S. Environmental Protection Agency (EPA) for fifteen years; as chair of EPA's Reference Dose (RfD) Work Group, charter member of the EPA's Risk Assessment Forum and chief of the group that helped create the Integrated Risk Information System (IRIS) in 1986. Dr. Dourson received his Ph.D. in Toxicology from the University of Cincinnati and a B.A. in biology from Wittenberg University. Dr. Dourson's research interests include investigating methods to extrapolate toxicity data garnered on experimental animals or healthy adults to the appropriate sensitive human population. Topics such as adversity of effect and characterization of risk are also of interest.

Dr. Dourson has served on numerous expert panels, such as EPA's peer review panels for IRIS assessments and its Risk Assessment Forum, *TERA*'s International Toxicity Estimates for Risk (*ITER*) independent peer reviews and consultations, FDA's Science Board Subcommittee on Toxicology, the National Science Foundation's Health Advisory Board, and the Society of Toxicology's harmonization of cancer and non-cancer risk assessment. Dr. Dourson has also organized over 16 symposia for 9 different organizations on a variety of topics, including: risk communication; chromium; information resources for toxicology and environmental health; risk assessment of essential trace elements; risk characterization; EPA's IRIS; uncertainty in risk assessment techniques; statistical and dose response models in risk assessment; workshop on benchmark dose methodology; basics of risk assessment; improvements in quantitative noncancer risk assessment; and neurotoxicity risk assessment.

Dr. Dourson is a Diplomate of the American Board of Toxicology and served on its Board as President, Vice President, and Treasurer. He is the past Secretary for the Society for Risk Analysis, and has also served as presidents of the Dose-Response Specialty Group of the Society for Risk Analysis, of the Society of Toxicology's Specialty Section on Risk Assessment and of the Ohio Chapter of the Society for Risk Analysis. He is also a member of the Academy of Toxicological Sciences, and currently on the editorial board of two journals. Dr. Dourson has published more than 100 papers on risk assessment methods, has co-authored well over 100 government risk assessment documents, and has made over 100 invited presentations.

Dr. Dourson is a core panel member. He was selected for the core panel because of his expertise in toxicology, risk assessment, and derivation of non-cancer risk values.

Disclosure

Dr. Dourson is Director of *TERA*. Dr. Dourson's employer (*TERA*) has performed work for companies, organizations, and contributing consultants associated with VCCEP; however, none of the work *TERA* did with these groups was on p-dioxane. In 2003 he reviewed EPA's Air Toxics Research Plan and Multiple Year Strategy documents, which may have included p-dioxane.

TERA has determined that Dr. Dourson has no conflicts of interest. His activity with EPA and his employer's work with some VCCEP sponsors are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Dourson's scientific objectivity as a VCCEP p-dioxane panel member.

Dr. John Bukowski

Dr. Bukowski is a senior associate at WordsWorld Consulting, a public health and medical-communications consultancy located in Dayton, Ohio. He provides research assistance on epidemiology and public/occupational health, as well as general assistance on issues relating to clinical medicine. WordsWorld provides contract assistance for a variety of organizations, including universities, other consulting groups, professional associations, research hospitals, pharmaceutical companies, and the petrochemical industry.

Dr. Bukowski has 20 years of experience in epidemiology and public health, which includes service within government, academia, and private industry. Prior to joining WordsWorld, he was a senior scientist and epidemiologist for ExxonMobil Biomedical Sciences, focusing on such varied topics as children's health, reproductive health, neurological health, solvent exposure, risk assessment, and emerging health issues. He has also served as a research scientist within both the New Jersey Department of Environmental Protection (NJDEP) and the U.S. EPA.

Dr. Bukowski has a broad range of clinical experience, including 7 years as a practicing veterinarian and service as the Director of the Clinical Research Centre at the University of Prince Edward Island, Canada. At UPEI, he oversaw all clinical and environmental research for the CRC, including a series of case-control studies on the associations between clinical birth outcomes and agricultural contamination of PEI ground water. He also authored several major reports for provincial organization, including a report to the PEI Cancer Research Council on the carcinogenic potential of agricultural pesticides applied on the Island.

Dr. Bukowski's background in risk assessment includes a position within the Risk Assessment Unit of the Division of Science and Research at NJDEP. He has published several papers on risk assessment theory and practice, and organized and chaired a symposium at the 2004 meeting of the Society for Risk Analysis.

Dr. Bukowski has served on several expert panels and professional committees. He was chairman of the PEI Pesticide Advisory Council, which is a formal provincial committee that makes recommendations directly to the Minister of Agriculture and Forestry. He has also served as the technical secretary for the ExxonMobil Occupational Exposure Limit (OEL) committee and as coordinator for both the Pesticide Review Committee and the Chromium Task Force at NJDEP. He has provided expert testimony to the U.S. EPA Clean Air Scientific Advisory Committee on air pollution issues and to the American Conference of Governmental Industrial Hygienists (ACGIH) on the health effects of mineral oils.

Dr. Bukowski holds a doctorate in veterinary medicine from Michigan State University. He also holds a Masters in Public Health from the University of Michigan, and a Ph.D. in epidemiology from the University of Medicine and Dentistry of New Jersey. He has authored numerous peer-reviewed articles as well as a multitude of reports, critiques, reviews, and white papers. He sits on the Editorial Board for the journal Dose-Response, and was an adjunct Associate Professor at the University of Medicine and Dentistry of New Jersey for many years.

Dr. Bukowski is an *ad hoc* panel member. He was selected for the p-dioxane panel because of his expertise in the areas of epidemiology, risk assessment, children's health, and the health effects of solvents.

Disclosure

None

TERA has determined that Dr. Bukowski has no conflicts of interest.

Dr. John Christopher

Dr. Christopher is a staff toxicologist with the Department of Toxic Substances Control (DTSC), California Environmental Protection Agency (Cal EPA). In this position he reviews, critiques, and approves assessments of risk to human health and ecological risk assessments at military facilities and other hazardous waste sites and permitted facilities in California. He constructs multi-pathway risk assessments to identify numerical criteria for classifying hazardous levels of metals and organic chemicals in waste. He also uses Monte Carlo methods in various exposure settings to identify levels protective of human health. He has received Certificates of Recognition for contributions resulting in the successful transfer of a hazardous waste landfill at a former naval shipyard in Vallejo, California, for a prescribed burn to uncover unexploded ordnance at a former fort in Monterey, California, and also for cleanup of a fleet industrial supply center in Alameda, California. In addition, he has received a Sustained Superior Accomplishment Award from California Department of Toxic Substances Control for risk assessment of metals in hazardous waste.

Prior to his current position with the State of California, Dr. Christopher conducted risk assessments for ICF Kaiser Engineers and IT Corporation. He also worked for research laboratories where he conducted and managed animal studies.

Dr. Christopher earned a B.S. in Biology from Georgetown University, Washington D.C., and a M.A. in Pharmacology from Stanford University, Palo Alto, California. He received his Ph.D. in Biological Science from Oregon State University, Corvallis, Oregon.

Dr. Christopher is a Diplomate of the American Board of Toxicology and a former member of this Board. He has served as President and held several other offices in the Risk Assessment Specialty Section of the Society of Toxicology (SOT) and also in SOT's Northern California Chapter. He is a peer reviewer for *Toxicological Sciences*, *Risk Analysis*, *Human and Ecological Risk Assessment*, and *CRC Critical Reviews in Toxicology*.

Dr. Christopher is a core panel member. He was selected for the core panel because of his experience in toxicology, multi-pathway risk assessment, and the evaluation of general and site-specific exposure scenarios.

Disclosure

Dr. Christopher's current responsibilities at Cal EPA include evaluating exposures from hazardous waste sites that may contain p-dioxane. In his regulatory capacity, he requires authors of risk assessments submitted to DTSC to use the values for toxicity of p-dioxane maintained by Cal EPA and the Integrated Risk Information System (IRIS) maintained by the U.S. Environmental Protection Agency. Because of these job-related responsibilities, Dr. Christopher requested the following statement in this disclosure: "Dr. Christopher performs scientific peer consultation for *TERA* as a private individual. His employer, the California Department of Toxic Substances Control, is not bound in any way by the opinions he expresses or by consensus agreements to which he chooses to be a party."

TERA has determined that Dr. Christopher has no conflicts of interest. His current responsibilities at Cal EPA are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Christopher's scientific objectivity as a VCCEP p-dioxane panel member.

Dr. John DeSesso

Dr. DeSesso is a charter member of the technical staff of Noblis (formerly Mitretek Systems), an independent, not-for-profit company that was formed from several parts of The MITRE Corporation. Dr. DeSesso is a Senior Fellow and the Director of the Biomedical Research Institute at Noblis. Dr. DeSesso has extensive experience in reproductive and developmental toxicity, risk assessment, ecological risk assessment, and the use of bioavailability in risk assessments.

Dr. DeSesso received his Ph.D. in Anatomy and Teratology from the Medical College of Virginia at Virginia Commonwealth University. He is a Diplomate of the American Board of Forensic Examiners and the American Board of Forensic Medicine, specializing in anatomy and risk assessment, and a Fellow of the Academy of Toxicological Sciences. Prior to joining Noblis, Dr. DeSesso was a Senior Principal Scientist at MITRE Corporation where he evaluated chronic studies (with special attention to reproductive toxicity and teratology) for the U.S. Environmental Protection Agency's (EPA) Office of Pesticides, conducted biostatistical analyses of data and risk assessment techniques, predicted toxic effects based upon structure-activity relationships for new chemicals, provided quality assurance of risk assessments performed by contractors for the U.S. Air Force, and performed independent research into the mechanisms that underlie chemically induced birth defects. Dr. DeSesso's research focus has been the elucidation of the mechanisms underlying teratogenesis and designing strategies to ameliorate the untoward effects.

Dr. DeSesso is currently a faculty member at Georgetown University School of Medicine, Rosalind Franklin University of Medicine and Science, San Diego State University Graduate School of Public Health, and the University of North Texas Health Sciences Center. He is an active member of numerous scientific societies where he has held various office positions, such as the Academy of Toxicological Sciences, the American College of Toxicology, the American Society for Reproductive Medicine, the Society for Risk Analysis, the Society of Toxicology, and the Teratology Society.

Dr. DeSesso has been an active member of the peer-review process reviewing manuscripts for major journals and grant proposals on a national and international level (e.g., EPA, United States-Israel Binational Science Foundation, National Institutes of Health, National Institute for Environmental Health Sciences [NIEHS]). He has been invited frequently to serve as the chairman of scientific sessions at national and international scientific meetings, especially those involving mechanisms or amelioration of developmental toxicity and ecological risk assessment. He has served as an invited faculty member or invited participant on many panels, refresher courses, and working groups that have been sponsored by a variety of federal agencies (e.g., EPA, U.S. Food and Drug Administration, NIEHS) and professional societies (e.g., Teratology Society, Toxicology Forum, American College of Veterinary Pathologists, Society of Environmental Toxicology and Chemistry, American College of Toxicology). Dr. DeSesso is on the editorial board of *Reproductive Toxicology*. He has published extensively in his areas of expertise, with his publications numbering well over 100.

Dr. DeSesso is a core panel member. He was selected for the core panel because of his experience in reproductive and developmental toxicity, in teratology, and in risk assessment.

Disclosure

None

TERA has determined that Dr. DeSesso has no conflicts of interest.

Dr. Gary Ginsberg

Dr. Ginsberg is currently a toxicologist at the Connecticut Department of Public Health within the Division of Environmental Epidemiology and Occupational Health. He has primary responsibility for human health risk assessments conducted across state agencies. He is also the project manager for several cooperative agreements with U.S. EPA. One project is researching pharmacokinetic differences between children and adults while the other is exploring the influence of genetic polymorphisms on susceptibility to toxicants and inter-individual variability.

Dr. Ginsberg serves as adjunct faculty at the Yale School of Medicine and is an Assistant Clinical Professor at the University of Connecticut School of Medicine. He recently finished serving on the National Academy of Science Panel on Biomonitoring, and he currently serves on the National Academy of Sciences panel that is evaluating U.S. EPA risk methods. He received his Ph.D. in toxicology from the University of Connecticut (Storrs) and was a post-doctoral fellow in carcinogenesis/mutagenesis at the Coriell Institute for Medical Research.

Dr. Ginsberg's toxicology experience has involved a variety of settings: basic research, teaching, working within the pesticide and consulting industries, and now working in public health. He has published in the areas of toxicology, carcinogenesis, physiologically-based pharmacokinetic modeling, inter-individual variability and children's risk assessment. He is also co-author of a book on toxics for the lay public, "What's Toxic, What's Not:" Berkley Books, December 2006.

Dr. Ginsberg is an *ad hoc* panel member. He was selected for the p-dioxane panel because of his expertise in the areas of risk assessment, carcinogenesis, and the pharmacokinetic differences between children and adults.

Disclosure

Dr. Ginsberg's current responsibilities at the Connecticut Department of Public Health may include evaluating exposures to p-dioxane; however, he is performing this scientific peer consultation for *TERA* as a private individual. His employer is not bound in any way by the opinions he expresses during the VCCEP p-dioxane discussions

TERA has determined that Dr. Ginsberg has no conflicts of interest. His current responsibilities at the Connecticut Department of Public Health are being disclosed to assure transparency. *TERA* does not believe these activities will impair Dr. Ginsberg's scientific objectivity as a VCCEP p-dioxane panel member.

Dr. Pertti (Bert) Hakkinen

Dr. Hakkinen is a Principal of the Gradient Corporation, and leads its Product Safety and REACH (Registration, Evaluation, Authorization, and Restriction of Chemicals) practices. Formerly, he was on the staff of the European Commission (EC) at the EC Joint Research Centre in the Physical and Chemical Exposure Unit of the Institute for Health and Consumer Protection. While at the EC, he helped develop and manage work packages for EIS-ChemRisks, the European Information System on risks from chemicals released from consumer products and articles (textiles, toys, etc.).

Dr. Hakkinen is a member of the Scientific Advisory Panel of the (U.S.) Mickey Leland National Urban Air Toxics Research Center and has served as the vice chair of this panel since March 2003. Prior to joining the EC staff, Dr. Hakkinen was on the staff of Toxicology Excellence for Risk Assessment (TERA). Before joining TERA, he worked at the Procter & Gamble Company to provide global human exposure and risk assessment support for numerous types of consumer products and chemicals. While at Procter & Gamble, he chaired the Exposure Assessment Task Group of the Chemical Manufacturers Association (now the American Chemistry Council [ACC]) for several years, and was a chair of the ACC's Human Exposure Assessment Technical Implementation Panel.

Dr. Hakkinen earned a B.A. in Biochemistry and Molecular Biology from the University of California, Santa Barbara, and received his Ph.D. in Comparative Pharmacology and Toxicology from the University of California, San Francisco. He served as a postdoctoral investigator in respiratory toxicology, and exposure and risk assessment at the Biology Division of the Oak Ridge National Laboratory. Dr. Hakkinen has been an invited expert or reviewer for the U.S. EPA, Health Canada, and other associations to develop or revise human exposure assessment guidance, resource documents, and software. He has lectured on exposure and risk assessment, risk perception, and risk communication at the University of Cincinnati and elsewhere.

Dr. Hakkinen is a member of the Society of Toxicology (SOT) and a charter member of the Society for Risk Analysis (SRA) and the International Society of Exposure Analysis (ISEA). He proposed the idea for the *Residential Exposure Assessment: A Sourcebook*, developed and published in 2001 via the expertise and involvement of members of SRA's Exposure Assessment Specialty Group, ISEA members, and many others. Dr. Hakkinen received SRA's Outstanding Service Award in 1996. He was on the editorial board of *Toxicology* and was a co-editor and co-author of the latest edition of *Information Resources in Toxicology* and is a co-editor and co-author of the new edition under development. Further, he is a co-editor and co-author of the latest edition (2005) of the *Encyclopedia of Toxicology*. Dr. Hakkinen has authored and co-authored numerous other publications, including ones on consumer product exposure and risk assessments, consumer risk perceptions, toxicological interactions, respiratory tract toxicology, and computer software and databases.

Dr. Hakkinen is a core panel member. He was selected for the core panel because of his experience in evaluating chemical exposures, especially to consumer product ingredients, and also because of his experience in toxicology and risk assessment.

Disclosure

None

TERA has determined that Dr. Hakkinen has no conflicts of interest.

Dr. Michael Jayjock

Dr. Jayjock is a Senior Analyst with The LifeLine Group, a non-profit organization dedicated to the development of scientific tools for human exposure and risk assessment. He has been with LifeLine for 3 years. Previous to this he was a Senior Research and Environmental Health and Safety Fellow and Manager for Risk Assessment at the Rohm and Haas Company; and had been working with that company for 35 years. In his current position, he is responsible for the determination of human health risk from and development of tools for the evaluation of human exposure and risk to chemicals.

Dr. Jayjock received both his Ph.D. in Environmental Engineering and his M.S. in Environmental Science and Occupational Health from Drexel University. He is a Fellow of the American Industrial Hygiene Association and is certified in the Comprehensive Practice of Industrial Hygiene by the American Board of Industrial Hygiene.

Dr. Jayjock's professional activities include such areas as exposure modeling research, human exposure and risk assessment to environmental pollutants, and uncertainty analysis. He has published extensively in peer-reviewed publications and served from 1998-2003 as an Editorial Board Member for the *American Industrial Hygiene Journal*. He has made numerous technical presentations, including at the American Industrial Hygiene Conference, International Society of Exposure Assessment Conference, and the Air Toxics Monitoring Workshop to Support the U.S. Environmental Protection Agency's (EPA) Integrated Urban Air Toxics Strategy. His wide service on advisory committees includes: EPA Board of Scientific Councilors Peer Review Panel for Office of Research and Development Science Program, Executive Committee, Human Health Research Strategy Panel; Voluntary Children's Chemical Evaluation Program (VCCEP), Peer Consultation Panels on Flame Retardants, Methyl Ethyl Ketone and Ethylbenzene; EPA Science Advisory Board, Executive Committee, Human Health Research Strategy Panel; EPA Science Advisory Board Consultant - Integrated Human Exposure Committee; EPA Science Advisory Board Member - Integrated Human Exposure Committee (IHEC); and National Research Council - National Academy of Sciences, as a Member of the Committee to Review Risk Management in the U.S. Department of Energy's (DOE) Environmental Remediation Program, the Committee on Advances in Assessing Human Exposure to Airborne Pollutants, and the Committee on Toxicology – Subcommittee on Risk Assessment of Flame-Retardant Chemicals.

Dr. Jayjock also serves as a team teacher or guest lecturer for local universities including Drexel, the Philadelphia University of the Sciences, Temple University, and Thomas Jefferson University. He is a guest lecturer at the University of Pennsylvania Medical School, Residency Program for Occupational Medicine; and he is also an instructor for a professional development course on risk assessment for the American Industrial Hygiene Conference and Exposition. Previously, he served as course director and instructor for Risk Assessment and Intermediate Exposure Modeling at the University of North Carolina Education Research Center, Summer Institute.

Dr. Jayjock is an *ad hoc* panel member. He was selected for the p-dioxane panel because of his expertise and experience in using multiple tools to determine chemical exposures and applying the findings to human risk assessment.

Disclosure

None

TERA has determined that Dr. Jayjock has no conflicts of interest.

Dr. Sam Kacew

Dr. Sam Kacew is Associate Director, Toxicology, McLaughlin Centre for Population Health Risk Assessment, Institute of Population Health, and he is Professor in the Department of Cellular and Molecular Medicine, Faculty of Medicine at the University of Ottawa. His responsibilities include teaching medical students and graduate students the techniques required to write and publish peer-reviewed papers. His current research involves the effects of chemical contaminants in breast milk on infants, the role of confounding factors in toxicity testing, and the basis for differences in responsiveness to chemicals between infants and adults.

Dr. Kacew received his Ph.D. in Pharmacology from the University of Ottawa. He served as a Postdoctoral Fellow for the Medical Research Council of Canada at the University of Montreal. Dr. Kacew was certified in 1994 as a Fellow of the Academy of Toxicological Sciences. He has received numerous awards, including several achievement, recognition, public communications, and travel awards from the Society of Toxicology (SOT), the United States-China Foundation, and the National Science Council of the Republic of China.

Dr. Kacew has served on numerous expert panels and committees, including: membership on the National Advisory Committee on Environmental Contaminants and the Implications for Child Health; the National Academy of Sciences (U.S.) Committee on Toxicology; Chair of the National Academy of Sciences Subcommittee on Iodotrifluoromethane; Chair of the National Academy of Sciences Committee on Tetrachloroethylene; and Co-chair for the U.S. EPA Workshop on Children's Inhalation Dosimetry. Dr. Kacew is serving on the Board of Directors of *TERA*. He also has served as a chairman for a variety of symposiums, panels, and committees including the SOT Annual Meeting's General Toxicology Session, the Federation of American Societies for Experimental Biology Annual Meeting, an Assessment Panel for the Canadian Council on Animal Care, a SOT Symposium on Use of Moderate Dietary Restriction in Safety Assessment, and an SOT Symposium on the Role of Diet and Obesity in Endocrine Disruption. He has presented hundreds of invited lectures for a variety of federal and state government agencies, colleges and universities, private companies, and international organizations. He was an invited participant to the American Society for Pharmacology and Experimental Therapeutics Meeting, the Federation of American Societies for Experimental Biology Annual Meeting, the International Life Sciences Institute, the Chalk River Nuclear Labs, the Turkey Society of Biochemistry, the Society of Toxicology of Taiwan, and the Korea Society of Toxicology. Dr. Kacew serves on the Board of Trustees for Toxicology Excellence for Risk Assessment (*TERA*).

Dr. Kacew is on a number of grant committees and has served as an external referee for grants and fellowships for a wide variety of organizations and government agencies. He is currently the Editor-in-Chief for the Journal of Toxicology and Environmental Health, the North American Editor of Toxicology and Environmental Chemistry, an Associate Editor for Toxicology and Applied Pharmacology, a Guest Editor for the Toxicology and Applied Pharmacology special issue on Toxicological Reviews in Fetal Childhood Development, as well as a member of the editorial board of a number of other journals. Dr. Kacew has over 140 publications in peer-reviewed journals and books in the area of toxicology, risk assessment, and children's health. He has also served as an editor for a number of books on toxicology and children.

Dr. Kacew is a core panel member. He was selected for the core panel because of his experience in toxicology and risk assessment, as well as his familiarity with the potential impact of environmental contaminants on children's health.

Disclosure

None

TERA has determined that Dr. Kacew has no conflicts of interest.

Dr. John Lipscomb

Dr. Lipscomb is a toxicologist with the U.S. EPA, Office of Research and Development, National Center for Environmental Assessment. His responsibilities at the agency involve the development and assessment of refined risk assessment methods, including evaluation of toxic mechanisms of action, dose-response assessments, exposure quantifications, and definitions of intrinsic modifiers of toxicity. He also reviews methods and guidelines related to the toxicological effects of environmental pollutants.

Dr. Lipscomb received his B.S. and M.S. degrees in Biology from the University of Central Arkansas and his Ph.D. degree in Interdisciplinary Toxicology from the University of Arkansas for Medical Sciences. Prior to joining EPA, he served as Captain in the U.S. Air Force and Chief of the Metabolism Section in the Toxicology Division of the Armstrong Laboratory at Wright- Patterson Air Force Base. While in that assignment, he designed and conducted research in xenobiotic metabolism in response to Air Force environmental and occupational health needs, determined the enzymological basis for human inter-individual and species-dependent differences in bioactivation, and identified potential modifiers of toxicity.

Dr. Lipscomb currently is an Associate Editor for Toxicological Sciences, serves on the editorial board for Toxicology Mechanisms and Methods, is an Adjunct Assistant Professor in the Department of Therapeutics, College of Pharmacy, University of Cincinnati, and also in the School of Public Health and Tropical Medicine, Department of Biological Sciences, Tulane University. He has been a Diplomate of the American Board of Toxicology since 1995 and serves on its Board of Directors.

Dr. Lipscomb is a member of the Society of Toxicology, the Society for Risk Analysis, and the International Society for the Study of Xenobiotics. He also is past and present office-holder in the regional chapters and specialty sections of these organizations. He has received numerous achievement awards and medals from the U.S. Air Force, Army, EPA and the National Institute for Occupational Safety and Health. In 2000, 2002 and 2003 he received awards from the SOT Risk Assessment Specialty Section for Outstanding Poster and Platform Presentations, Best Abstract, and Top Ten Best Papers, and in 2004 from the journal, Human and Ecological Risk Assessment for the outstanding paper on human health risk assessment.

Dr. Lipscomb is an *ad hoc* panel member. He was selected for the p-dioxane panel because of his expertise in PBPK modeling and in risk assessment.

Disclosure

Dr. Lipscomb is employed by the U.S. EPA, which has taken public positions on the VCCEP pilot chemicals, including p-dioxane.

TERA has determined that Dr. Lipscomb has no conflicts of interest. The comments that Dr. Lipscomb makes during this meeting are his personal opinions and should not be construed to represent the opinions of the U.S. EPA.

Dr. Earle Nestmann

Dr. Nestmann is a toxicologist with extensive experience in regulatory issues and risk assessment. Prior to joining Cantox, he was a research scientist at Health Canada in the Health Protection Branch. At Health Canada, Dr. Nestmann was responsible for a laboratory program in genetic toxicology and contributed to the development of regulatory policies for the use of genotoxicity data and for assessment of potential risk from genetically engineered micro-organisms. As the Canadian Manager of Regulatory and Environmental Affairs for Cyanamid Canada and at Cantox, Dr. Nestmann has gained experience applicable to the development and evaluation of safety programs for pesticides, food additives, GRAS substances, pharmaceuticals, industrial chemicals, and other products and materials.

Dr. Nestmann received M.Sc. and Ph.D. degrees from York University for work in microbial genetics, chemical mutagenesis, spontaneous mutation, and anti-mutagenesis. Later, as an Assistant Professor of Biology at York University, he taught courses including genetics, microbiology, and natural and environmental sciences.

As a member of several national and international committees and panels, Dr. Nestmann has worked with the World Health Organization, the U.S. National Toxicology Program, the U.S. National Academy of Sciences, the Natural Sciences and Engineering Research Council, and a number of trade associations. He also has served as the President of the Genetics Society of Canada, is on the Board of Trustees of the American Type Culture Collection, and is a member of the Board of Directors for York University Alumni Association. Dr. Nestmann has edited several books on risk assessment and recombinant DNA methodology. He has published more than 150 scientific papers in the fields of microbial genetics, mutagenesis, toxicological evaluation, product regulation, and risk assessment.

Dr. Nestmann is an *ad hoc* panel member. He was selected for the p-dioxane panel because of his expertise and experience in genetic toxicology and in risk assessment.

Disclosure

None

TERA has determined that Dr. Nestmann has no conflicts of interest.

Ms. Ruthann Rudel

Ms. Ruthann Rudel is a Senior Scientist responsible for toxicology and environmental risk assessment for the Silent Spring Institute. She manages the toxicology and environmental exposure components of the multi-disciplinary Cape Cod Breast Cancer and Environment Study. For this study, Ms. Rudel designs and manages investigations of the hypothesis that exposure to endocrine disruptors might play a role in breast cancer etiology. Her work includes designing and managing field sampling programs and developing exposure variables, as well as managing work with study collaborators with at Tufts Medical School, Harvard University School of Public Health, and other institutions. She has considerable experience in risk assessment of environmental chemicals.

Prior to joining the Silent Spring Institute, Ms. Rudel worked as an environmental toxicologist for Gradient Corporation. As such, she evaluated the health effects of exposure to hazardous chemicals in the environment in order to provide a sound basis for environmental management decisions. She reviewed international properties contaminated with pesticides and chlorinated solvents, and evaluated blood biomarkers and exposure from inhalation, soil and dust ingestion and bioconcentration, and fish ingestion. In addition, Ms. Rudel also worked as an Editor for World Information Systems where she researched, wrote and edited a national weekly newsletter entitled, *Hazardous Materials Intelligence Report*.

Ms. Rudel received her M.S. in Hazardous Materials Management from Tufts University and has completed graduate coursework at the Harvard Extension School and the New England Epidemiology Institute. She also received a B.A. in Chemistry with High Honors in Neuroscience from Oberlin College.

Ms. Rudel's professional activities include membership in numerous scientific societies and participation as a reviewer for journals and on peer review panels. Ms. Rudel is a member of the Society of Toxicology, Society for Risk Analysis, and the International Society for Exposure Analysis. She is an *ad hoc* manuscript reviewer for four scientific journals on toxicology, environmental health, and environmental science. She has participated as a reviewer for various government, non-profit, and academic organizations. She also has numerous publications and presentations in the areas of exposure assessment, geographic information systems (GIS), and endocrine disruptors.

Ms. Rudel is an *ad hoc* panel member. She was selected for the p-dioxane panel because of her expertise and experience in carcinogenesis and endocrine toxicology, in identifying exposure sources, and in environmental and human risk assessment.

Disclosure

None

TERA has determined that Ms. Rudel has no conflicts of interest.

Dr. Chad Sandusky

Dr. Sandusky is currently Director of Toxicology and Research at the Physicians Committee for Responsible Medicine (PCRM), a non-profit organization that promotes good nutrition, conducts clinical trials and promotes and develops non-animal experimental methods in medical and scientific research. For PCRM, Dr. Sandusky coordinates the review and preparation of comments on the EPA's High Production Volume Challenge Program (HPV) and Voluntary Children's Chemical Evaluation Program (VCCEP) chemical assessments. As such, he stresses the weight-of-evidence approach in these assessments and the development of exposure scenarios as key to the success of these programs. He is actively engaged in identifying methods, which use alternatives to animal testing to meet the needs of the safety assessments, including tests undergoing validation at the European Center for Alternative Methods (ECVAM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).

Dr. Sandusky was a past Manager of Toxicology and Risk Assessment at ENVIRON and has extensive experience at both the EPA and ENVIRON in pesticide toxicology as well as exposure and risk assessments. For example, he evaluated the toxicology of pesticides and extrapolated these effects in risk assessments; directed the dietary exposure and risk assessments for agrochemicals and other potentially toxic residues in foods using the TAS Dietary exposure software; served as toxicology team leader and senior author of numerous EPA documents, including Registrations Standards and Position Documents; and since the passage of the FQPA in August 1996, coordinated the review and assessment of numerous agrochemicals to address the full range of new requirements, including: assessing aggregate exposure from multiple pathways (e.g., drinking water and residential use), cumulative exposure to chemicals with a common mode of action, accounting for potential sensitivity to infants and children, and assessing the potential for endocrine disruption.

Dr. Sandusky has extensive international experience including the coordination and submission of dossiers for the EU Reauthorization process under EU 91/414 and presentation of the results to member states. Dr. Sandusky also represented the Institute of Food Technology at the Codex Committee for Pesticide Residues (CCPR) in The Hague for several years. In addition, he also coordinated preparation and reviews of dossiers for chemicals approved as GRAS as well as directed the preparation and submission of Food Contact Notifications (FCNs) to the FDA.

For the past four years, Dr. Sandusky represented the International Council of Animal Protection Organizations (ICAPO) at OECD meetings in Paris, Tokyo and Bern on the Existing Chemicals Programme. At present, PCRM, with Dr. Sandusky as lead, serves as Secretariat to ICAPO, and coordinates participation of all ICAPO member organizations (from North America, the EU, and Japan) and their consultants in numerous expert work groups, international task forces on chemical hazard testing and has liaised with the US Ambassador to OECD.

Dr. Sandusky received his Ph.D. in Pharmacology from the Emory University. He served as a Postdoctoral Fellow at the Georgetown University Schools of Medicine and Dentistry, Washington, D.C. He is currently a member of the Society of Toxicology, and he was previously affiliated with such organizations as the International Society of Exposure Analysis and the Society of Environmental Toxicology and Chemistry. Dr. Sandusky serves on the Board of Trustees of Toxicology Excellence for Risk Assessment (*TERA*).

Dr. Sandusky is a core panel member. He was selected for the core panel because of his expertise in toxicology and pharmacology, in risk assessment, and his extensive knowledge of animal welfare issues.

Disclosure

Dr. Sandusky's employer, Physicians Committee for Responsible Medicine (PCRM), has submitted comments on High Production Volume (HPV) test plans submitted to the U.S. EPA by Ferro Corporation, Inc.

TERA has determined that Dr. Sandusky has no conflicts of interest. PCRM routinely submits comments on HPV chemicals. The comments that Dr. Sandusky makes during this meeting are his personal opinions and should not be construed to represent the opinions of PCRM.

Dr. Susan Hunter Youngren

Dr. Susan Youngren is a Senior Managing Scientist with the legal firm of Bergeson & Campbell, PC. Prior to joining Bergeson & Campbell, she held a similar position with Exponent, Inc. (formerly Novigen Sciences, Inc.). Her previous assignments include positions at EA Engineering, Science, and Technology, Inc, and the ILSI Risk Science Institute. Dr. Youngren is responsible for assessing a variety of scientific issues for the clients of Bergeson & Campbell, PC for both regulatory actions as well as product stewardship. This work ranges from assessments for registration and re-registration of pesticides to labeling issues for consumer products in the area of company responsibilities to their customers.

Dr. Youngren received her Ph.D. in Environmental Biology and Public Policy from George Mason University, her M.S. in Environmental Sciences and Engineering from the Virginia Polytechnic Institute and State University, and her B.S. in Microbiology and Public Health from Michigan State University.

Dr. Youngren has over 25 years experience in risk assessment, with particular emphasis on exposure assessment. She has conducted many types of risk assessments, such as residential, dietary, microbial, occupational, and hazardous waste sites. She has assessed dermal, oral, and inhalation exposures for paints, indoor and outdoor foggers, and for products used on carpets, turf, and home gardens. Her work has included development of project-specific algorithms, data analysis, determination of the applicability of surrogate data, development of distributional data, and complex distributional analysis.

Dr. Youngren is a member of the International Society of Exposure Analysis and is a former Councilor. She also belongs to the Society of Risk Analysis, the Society for Occupational and Environmental Health, and the American Association of University Women. She has numerous publications in the areas of risk assessment and exposure, such as a risk assessment for children playing on lawns treated with pesticide. She also has made many presentations on topics such as children's exposure to pet products, choosing distributional forms for use in Monte Carlo exposure assessments, and advancing exposure assessment in the residential environment.

Dr. Youngren is an *ad hoc* panel member. She was selected for the p-dioxane panel because of her expertise and experience in exposure source identification and assessment, and also in risk assessment.

Disclosure

None

TERA has determined that Dr Youngren has no conflicts of interest.

VCCEP p-Dioxane Peer Consultation Meeting

Presenter Biosketches

Dr. Michael Gargas

Managing Principal
The Sapphire Group

Michael L. Gargas, Ph.D., is a Managing Principal with *The Sapphire Group*, a risk assessment and risk management consulting firm. Dr. Gargas is a toxicologist with over 28 years of related environmental and health experience. He oversees and prepares human health risk assessments, conducts toxic tort support investigations, serves as an expert witness, interacts with regulatory agencies, and addresses critical toxicological issues through applied and basic research on behalf of clients. Dr. Gargas' area of expertise is in human health risk assessment and biochemical toxicology research with emphasis in the areas of inhalation toxicology, chemical metabolism, physiologically based pharmacokinetic (PBPK) modeling, and chemical dosimetry, with specific application of these approaches to risk assessments.

Dr. Gargas completed his doctorate in Biomedical Sciences (Toxicology Specialty) from Wright State University. He has been an active member in the Society of Toxicology since 1989 and the Society for Risk Analysis since 1992 and has served on the editorial board of *Toxicology and Applied Pharmacology*. He is a member and has served as a Councilor to the Risk Assessment Specialty Section of the SOT and is currently serving as the President of that Specialty Section. He has published seven book chapters and over 70 peer-reviewed articles on a wide range of health and toxicologic topics. Dr Gargas is also an Adjunct Assistant Professor of Toxicology in the School of Medicine at Wright State University, serving as director for a yearly graduate course in biokinetics and toxicology.

Mr. Richard Hubner

Managing Principal
The Sapphire Group

Richard P. Hubner, M.P.H., a co-founder and Managing Principal of *The Sapphire Group*, a risk assessment and risk management consulting firm. Mr. Hubner is a public health specialist and risk analyst with over fifteen years of experience in the fields of strategic risk management, toxicologic interpretations and research, in risk assessment/safety evaluation, research planning, regulatory affairs, industrial hygiene, and risk communication. Mr. Hubner has extensive experience in conducting field studies, exposure analysis, epidemiology, and statistics. Mr. Hubner performs detailed examinations of toxicity databases for numerous compounds present in air, drinking water, foods, consumer products, medical devices, the workplace, and waste products. He directs and conducts diverse human health and ecological risk assessments and his expertise extends to a wide range of substances including pesticides, occupational toxicants, consumer products, medical devices, and environmental contaminants in all environmental media. He provides guidance on product registrations, labeling requirements, MSDS warnings, and estimates risks of contaminants in consumer products and on regulatory compliance and risk communications. Mr. Hubner evaluates the health significance of occupational exposures to chemicals and other hazards. He examines the toxicity data used in the formulation of MSDS documents and develops site-specific health and safety, operational manuals, waste management plans, and spill containment procedures for varying sites including several for petrochemical companies, military facilities, and manufacturing facilities.

Mr. Hubner has completed degrees in the Biological Sciences from Rutgers University and a Masters in Public Health from the University of Medicine and Dentistry of New Jersey. In addition, Mr. Hubner holds certifications as an AHERA Asbestos Investigator, U.S. EPA Region II Organic Data Validator, and a North Carolina Certified Asbestos Investigator.

Mr. Alan Olson

Director of Technology and Product Stewardship; Organic Specialties Group
Ferro Corporation, Inc.

Alan is currently Director of Technology and Product Stewardship for the Organic Specialties Group of Ferro Corporation. Ferro has corporate headquarters in Cleveland, OH. The Ferro Organic Specialties Group manufactures and markets plastics, polymer additives, solvents, electrolytes and pharmaceutical intermediates globally. Alan is located at the Posnick Center of Innovative Technology in Independence, OH. He is responsible for product hazards communications (such as MSDS's,) product safety (such as FDA compliance, HPV submissions, product toxicological testing and risk assessments,) and coordinates programs for Responsible Care (EHS and security) and REACH. These responsibilities can be state, national or global in scope.

Before Ferro, Alan worked at BF Goodrich in technical, business management and regulatory roles for chemicals and plastics. Prior to that, he did development and test work on fuel cells at Pratt & Whitney.

Alan holds a Bachelor's Degree in Chemical Engineering from Tufts, and an MBA degree from the University of Connecticut. His education includes graduate work in environmental chemistry, polymer science, and R&D management. He has over 25 years experience in the chemicals and plastics industries.

Alan serves on the board of the Vinyl Institute in Washington, DC, and participates in a number of panels at the American Chemistry Council and SOCMA. Alan is currently Vice Chairman of the State of Ohio Board of Registration for Professional Engineers and Surveyors, and served two terms as president of the Ohio Society of Professional Engineers. Alan is currently a member of the American Chemical Society, the American Institute of Chemical Engineers, the National Society of Professional Engineers (past board member,) and the Ohio Academy of Science. Alan holds Professional Engineers licenses in Ohio (active) and Connecticut (inactive.)

Mr. Richard (Rick) Stalzer

Worldwide Director, Environmental, Health & Safety Consulting
Ferro Corporation, Inc.

In his position at Ferro, Rick is responsible for directing the Environmental Health and Safety (EHS) Consulting shared services group that is located at Ferro's Posnick Center of Innovative Technology. This group provides advice on relevant environmental, health and safety issues, develops EHS policies and tools for improved performance, and conducts EHS due diligence and technical service. He is the key advisor to senior management on all company EHS matters and supports the compliance activities at over 60 manufacturing plants in 20 countries.

Rick has thirty years of EHS experience, most of it with British Petroleum. He held various positions in increasing responsibility in research and development, engineering, and EHS during his twenty years there. In his last assignment at BP Chemicals he was Director of Health, Safety and Environmental Quality and was responsible for chemical company policy, issues and programs in the areas of occupational health, industrial hygiene, employee and product safety, customer and technical support, and environmental quality and research for their U.S. and international operations and products.

Rick has a Bachelor's Degree in Chemical Engineering from The University of Toledo, Ohio and a Master's Degree in Chemical Engineering from Cleveland State University. In the area of health, safety and environmental management, Rick has written numerous papers and chapters in books, and made many presentations on environmental technology and health and safety issues in both the U.S. and Europe. Rick participates in a number of industry trade associations and routinely works with government and non-government officials on EHS regulations, legislation and policy. He was a member of the Board of Directors of the Ground Water Protection Council from 1994-1999; Chairman of the Ohio Chamber of Commerce Energy and Environment Committee from 1990-1999; and a past Chairman of the Acrylonitrile Group Inc. Currently, Rick is on the Board of Directors for the Greater Cleveland Safety Council, the Storm Water Management Board for the City of Broadview Heights, OH, the Ohio Chamber's Executive Board to the Energy and Environment Committee, and a member of the American Institute of Chemical Engineers.

Appendix C

Voluntary Children's Chemical Evaluation Program (VCCEP) Peer Consultations on P-Dioxane May 1-2, 2007

Sponsors' Presentation Slides

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VCCEP Peer Consultation: Introduction for p-Dioxane

Alan Olson
Director of Technology and Product Stewardship
Ferro Corporation

1 May 2007



Outline of Presentations

Introduction:

Alan Olson, M.B.A., P.E., Ferro Corp.

Hazard Assessment:

Michael L. Gargas, Ph.D., The Sapphire Group
Richard P. Hubner, M.P.H., The Sapphire Group

Exposure Assessment:

Richard B. (Rick) Stalzer, M.S., Ferro Corp.
Richard P. Hubner, M.P.H., The Sapphire Group

Risk Characterization

Michael L. Gargas, Ph.D., The Sapphire Group
Richard P. Hubner, M.P.H., The Sapphire Group

Data Needs:

Richard P. Hubner, M.P.H., The Sapphire Group
Michael L. Gargas, Ph.D., The Sapphire Group

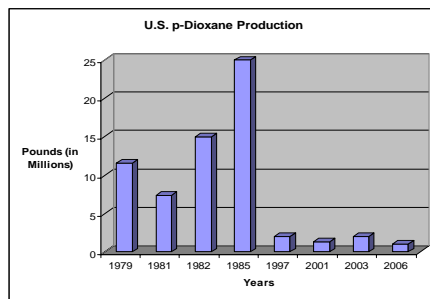
VCCEP Selection Basis

- ♦ Total Exposure Assessment Methodology (TEAM) Studies
 - California mid-1980's
 - Detected in breathe samples and outdoor and indoor air at the same location
- ♦ 1,4-Dioxane has been detected in:
 - Surface and ground water; drinking water
 - Outdoor, indoor and workplace air
 - Food (trace impurity, naturally occurring)
 - Consumer health care products (trace impurity)
- ♦ Per CDC, no current biomonitoring for 1,4-dioxane

Sources of 1,4-Dioxane

- ♦ Ferro is the only current US producer.
- ♦ Current uses: process solvent for chemical applications and as a pesticide carrier; minor uses in coatings and inks (limited by cost.)
- ♦ Historic uses: stabilizer for chlorinated solvents (1,1,1-trichloroethane,) dyestuff additive, wood pulping, fumigant and cleaner.
- ♦ Consumer products contain 1,4-dioxane as a by-product from ethoxylated chemicals in these products.
 - This 1,4-dioxane is unrelated to that produced by Ferro.
 - Not part of the 'chain of commerce' for commercially produced 1,4-dioxane

Montreal Protocol Banned 1,1,1 Trichlorethane in 1986 Leading to Reduced U.S. Production of p-Dioxane



Previous and Concurrent Assessments of 1,4-Dioxane

- ♦ IARC 1999
- ♦ NCI 1978
- ♦ IRIS 2002
- ♦ ATSDR 2006
- ♦ EU Risk Assessment 1996
- ♦ IPCS 1998
- ♦ NICNAS 1998
- ♦ NIOSH 1984
- ♦ NTP 2005
- ♦ Cal EPA 2000
- ♦ IRIS (Update)

Regulatory Overview of 1,4-Dioxane

- ♦ Clean Air Act
 - NESHAP: Listed hazardous air pollutant
 - NSPS: Subject to VOC emissions limits
- ♦ CERCLA
 - Reportable Quantity: 100 lb.
- ♦ Emergency Planning and Community RTK reporting obligations
- ♦ RCRA (hazardous waste)
- ♦ DOT – special requirements for labeling and transportation
- ♦ EPA - Lifetime Health Advisory Level
 - 0.7 mg/L at 1E-4 risk

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VCCEP Peer Consultation: Hazard Assessment for p-Dioxane

Michael L. Gargas, Ph.D.
The Sapphire Group

and

Richard P. Hubner, M.P.H.
The Sapphire Group

1 May 2007



VCCEP Studies

Tier 1	Tier 2	Tier 3
Acute toxicity	Subchronic toxicity	Neurotoxicity screening battery
Repeated dose toxicity with reproductive and developmental toxicity screens	Prenatal developmental toxicity Reproductive and fertility effects	Carcinogenicity
Bacterial reverse mutation assay	Immunotoxicity	Developmental neurotoxicity
<i>In vitro</i> or <i>in vivo</i> chromosomal aberrations or <i>in vivo</i> micronucleus test	<i>In vivo</i> chromosomal aberrations or <i>in vivo</i> micronucleus test	
	Metabolism and pharmacokinetics	

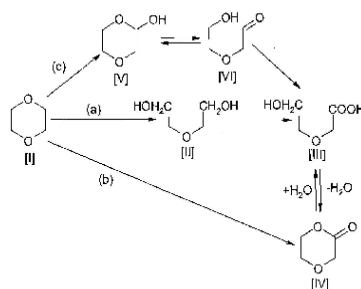
VCCEP – p-Dioxane Hazard Assessment: Tier 1

Tier 1	Health Effect Endpoint	Effect/No Effect Level
Acute toxicity	Mortality	Oral LD50 = 1,270-7,500 mg/kg Dermal LD50 = 7,600->8,300 mg/kg Inh LC50 = 37,000-65,000 mg/m ³
Repeated dose toxicity		Superseded by Tier 2 90-Day Subchronic Toxicity studies and Tier 3 Chronic Toxicity and Carcinogenicity studies
Bacterial reverse mutation assay	Mutations	Negative Results
<i>In vitro</i> chromosomal aberrations	Chromosome Damage	Weakly Positive for Sister Chromatid Exchanges and Negative for Chromosome Aberration in CHO cells,

VCCEP – p-Dioxane Hazard Assessment: Tier 2

Tier 2	Health Effect Endpoint	Effect/No Effect Level
Sub-acute and sub-chronic toxicity	Hepatic effects (including liver weights and gene expression);	Oral NOAEL = 10 mg/kg-d bw Oral LOAEL = 400 mg/kg-d bw
	No effects on growth, organ weights, hematology and clinical chemistry	Inhalation NOAEL = 108 mg/m ³
Prenatal developmental toxicity	Reduced maternal and fetal weight gain	NOAEL = 517 mg/kg-d
Reproductive and fertility effects	Reproductive effects	NOAEL = 1,033 mg/kg-d
Immunotoxicity		
<i>In vivo</i> micronucleus test	Chromosome damage	Variable results; primarily negative; LOAEL = 900 mg/kg
Metabolism and pharmacokinetics		Well absorbed from skin, lungs and GI tract, rapidly distributed in the body, metabolized primarily to HEAA and excreted principally in the urine

VCCEP – p-Dioxane Hazard Assessment: Metabolism



I = 1,4-dioxane; II = diethylene glycol; III = β-hydroxyethoxy acetic acid (HEAA); IV = 1,4-dioxane-2-one;
V = 1,4-dioxane-2-ol; VI = β-hydroxyethoxy acetaldehyde

VCCEP – p-Dioxane Hazard Assessment: Tier 3

Tier 3	Health Effect Endpoint	Effect/No Effect Level
Neurotoxicity screening battery	Changes in brain chemistry	LOAEL = 1,050 mg/kg
	Behavioral effects	NOAEL = 10,980 mg/m ³ LOAEL = 21,960 mg/m ³
Carcinogenicity	Liver tumors	NOAEL = 40 mg/kg-d
	Nasal tumors	NOAEL = 90-150 mg/kg-d (rats) NOAEL = 160-280 mg/kg-d (mice)
Developmental neurotoxicity		

VCCEP – p-Dioxane Hazard Assessment: Cancer MOA

- ♦ The weight-of-evidence indicates the cancer MOA for 1,4-dioxane is via cytotoxicity followed by cell proliferation and RDS
 - 1,4-Dioxane and major metabolite (1,4-dioxan-2-one) are not mutagenic
 - Tissue damage is observed at doses above metabolic saturation
 - Promotion of initiated cells and induction of P-450 enzymes may also play a role
 - Others have also reached this conclusion (NICNAS 1998; TNO 2002; Dietz *et al.* 1982; Stott *et al.* 1988; Hartung 1989; Reitz *et al.* 1990; Leung and Paustenbach 1990; Stickney *et al.* 2003)

VCCEP – p-Dioxane Hazard Assessment: Cancer MOA

- ♦ Nasal tumors result from splashing of drinking water containing 1,4-dioxane onto nasal turbinates resulting in cytotoxicity
- ♦ Liver tumors are the result of a non-genotoxic MOA most likely involving cytotoxicity

VCCEP – p-Dioxane Hazard Assessment Summary

- ♦ p-Dioxane toxicity is fairly well characterized with some data-gaps (immunotoxicity and developmental neurotoxicity)
 - Note update to ATSDR 2006 profile based on FDA comment:
<http://www.atsdr.cdc.gov/toxprofiles/tp187.html>
- ♦ Animal toxicity observed ≥ 10 mg/kg for non-cancer effects and ≥ 40 mg/kg-d for liver tumors from chronic studies
- ♦ The weight-of-evidence indicates that p-dioxane is most likely a non-genotoxic carcinogen acting via a cytotoxic MOA

VCCEP Peer Consultation: Exposure Assessment for p-Dioxane

Richard B. Stalzer, M.S.
Ferro Corporation

and

Richard P. Hubner, M.P.H.
The Sapphire Group

1 May 2007



Exposure Assessment Objectives

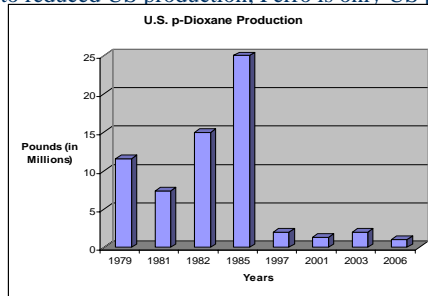
- ◆ Document sources and significant pathways of exposure for p-dioxane
- ◆ Develop conservative mean and 95th percentile exposure dose estimates for all pathways
- ◆ Identify all age-specific exposure variables

Sources of p-Dioxane – Commercial Uses

- ♦ A stabilizer for chlorinated solvents (particularly 1,1,1-trichloroethane)
- ♦ Process solvent for fire retardant chemicals
- ♦ Extraction solvent for fats, oils, waxes, & resins
- ♦ Carrier solvent for pesticides
- ♦ Minor uses – fumigant, wood pulping, dyes, lacquers, paints, varnishes, stains, printing compositions
- ♦ High cost for p-dioxane limits its use to high end, specialty or niche applications

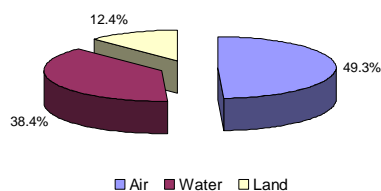
Sources of p-Dioxane – Commercial Production

- ♦ Banning of 1,1,1-trichloroethane under Montreal Protocol has lead to reduced US production; Ferro is only US producer



Sources of p-Dioxane Environmental

- ♦ 2004 TRI Releases – 233,349 lbs.
 - Releases are down 19% since 2000 and 47% since 1995



Other Sources of p-Dioxane

- ♦ Consumer Products (by-product of ethoxylation reactions from condensing ethylene oxide or ethylene glycol)
 - Detergents, shampoos, surfactants
 - Food additives
 - Stabilizers
 - Solubilizers
 - Surfactants
 - Emulsifiers
 - Food packaging
 - Adhesives
- ♦ Most of these “molecules” are not from the p-dioxane chain of commerce

Exposure Data Sources

♦ Occupational

- Personal sampling data from manufacturing, processing and end-use facilities
- Inhalation: 0.54 mg/m³; range 0 to 47 mg/m³ (100% abs)
- Dermal: 30 min.; range 0 to 2 hrs
40% p-dioxane; range 5%-100%

♦ Ambient (Indoor and Outdoor) air

- USEPA TEAM study (Wallace, 1987)
- Inhalation: 0.26 : g/m³; range 0 to 5.0 : g/m³ (100% abs)

Exposure Data Sources

♦ Breast milk

- PBPK model based on maternal exposure of 25 ppm (Fisher *et al.*, 1997)
- Ingestion: 0.56 mg/day (100% abs)

♦ Water

- Drinking water monitoring results
- Ingestion: 2 ppb; range 0.5 to 2,000 ppb
- Dermal (showering): 2 ppb; range 0.5 to 2,000 ppb

♦ Food

- FDA limit (< 10 ppm) for p-Dioxane as an impurity for all food
- p-Dioxane in Additives: 5 ppm; range 0 to 10 ppm
- Additives in Food: 0.1% of food; range 0.005% to 5%

Exposure Data Sources

♦ Consumer Products

- FDA limit for Cosmetic Products (shampoos, bath preparations, lotions) is <10 ppm
 - ♦ p-Dioxane Concentration: 10 ppm; range 0 to 500 ppm
 - ♦ Daily volume: 20 ml; range 0 to 50 ml
 - ♦ Infants: 4 hrs/day
 - ♦ Older children: 15 minutes/day; range 0 to 30 minutes/day

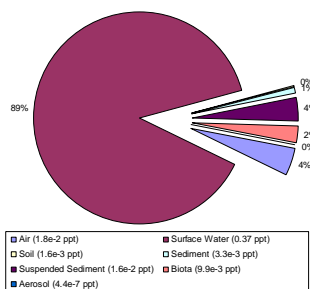
Environmental Transport and Partitioning

♦ MacKay Fugacity Modeling

- p-Dioxane data limited in scope
- Level II modeling conducted using default parameters
- Mesoscale estimate derived using data from the remaining US producer of p-Dioxane averaged over 5 years
- Entire production amount assumed to be released into environment

Environmental Transport and Partitioning

- ◆ Results indicate that potential exposure at steady state is low



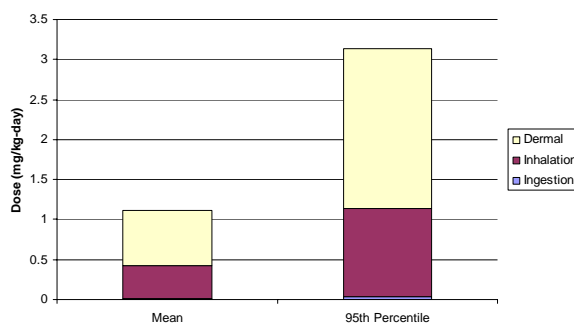
Receptor Populations

- ◆ Occupational: Pregnant worker (Fetus)
- ◆ Children (based on Child-Specific Exposure Factors Handbook [USEPA, 2006]):
 - 0-1 years
 - 1-2 years
 - 2-3 years
 - 3-6 years
 - 6-11 years
 - 11-16 years
 - 16-21 years

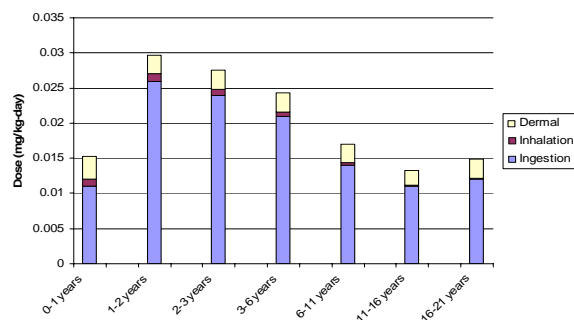
Exposure Pathways

Life-Stage	Ingested Water	Ingested Breast Milk	Ingested Food	Inhaled Air	Dermal Contact – Water	Dermal; Contact – Consumer Product	Dermal Contact - Solvent
Pregnant Worker (Fetus)	Yes (Mother)	No	Yes (Mother)	Yes (Mother)	Yes (Mother)	Yes (Mother)	Yes (Mother)
Infant (0-1)	No	Yes	Yes	Yes	Yes	Yes	No
Child: 1-2 yrs 2-3 yrs 3-6 yrs 6-11 yrs	Yes	No	Yes	Yes	Yes	Yes	No
Youth 11-16 yrs 16-21 yrs	Yes	No	Yes	Yes	Yes	Yes	No

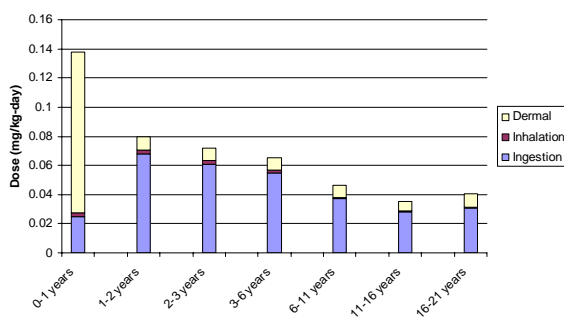
Mean and 95th Percentile Average Daily Dose Estimates – Pregnant Worker (Fetus)



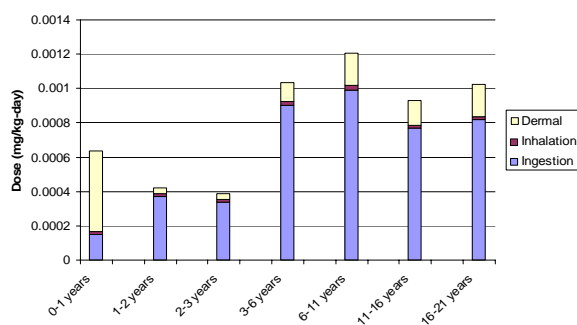
Mean Average Daily Dose Estimates - Children



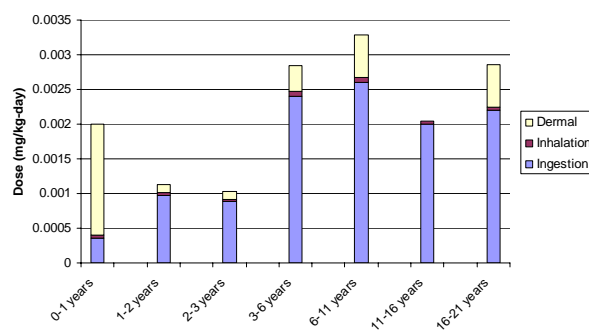
95th Percentile Average Daily Dose Estimates - Children



Mean Lifetime Average Daily Dose Estimates - Children



95th Percentile Lifetime Average Daily Dose Estimates - Children



Conclusions

- ♦ All Exposure Pathways relied on conservative approaches.
- ♦ For Pregnant Worker Scenario – dermal contact is the dominant exposure pathway
 - Direct solvent contact
- ♦ For All Children Scenarios – ingestion is the dominant exposure pathway
 - Infant dermal doses higher due to longer exposure to consumer products (i.e., lotions)
- ♦ Doses derived from fugacity modeling were 2 to 4 orders of magnitude below media specific and probabilistic forecasts

VCCEP Peer Consultation: Risk Characterization for p-Dioxane

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The Sapphire Group

and

Richard P. Hubner, M.P.H.
The Sapphire Group

2 May 2007



VCCEP – p-Dioxane Risk Characterization Overview

- ♦ PBPK modeling
- ♦ RfD Derivation
- ♦ RfC Derivation
- ♦ Risk Characterization for children and prospective parents
- ♦ Summary

Use of PBPK Models in p-Dioxane VCCEP Assessment

- ♦ Available PBPK models
 - Reitz *et al.* 1990; Leung and Paustenbach 1990; Balter 1989; Fisher *et al.* 1997
 - Update to Reitz *et al.* (see: Docket EPA-HQ-ORD-2003-0016 (submissions in support of on-going IRIS assessments of chemicals). Document numbers: EPA-HQ-ORD-2003-0016-0077.1 (PBPK) and -0078.1 (nasal splashing).
- ♦ Used Fisher model estimates for lactational exposure
- ♦ Used Reitz approach with linear extrapolation and internal doses for comparison purposes in cancer assessment
- ♦ Dose metrics for animals and humans from Reitz *et al.* used to inform regarding UFa

Oral RfD Derivation for p-Dioxane

- ♦ No RfD currently available
- ♦ Key Studies
 - Kociba *et al.* 1974
 - Yamazaki *et al.* 1994
- ♦ Key Effects
 - Liver and kidney toxicities (rats and mice)
 - Liver cancer (rats and mice)
- ♦ Overall NOAEL at 10 mg/kg-d
(liver cancer NOAEL at 40 mg/kg-d)
- ♦ Total UF=100 (UFh=10; UFa=3; UFd=3; UFc=1; UFl=1)
- ♦ Oral RfD = 0.1 mg/kg-d (also used for dermal RfD)

Reproductive/Developmental RfD Derivation for p-Dioxane

- ◆ Key Study
 - Giavini *et al.* 1985
- ◆ Key Effects
 - Slight maternal and embryotoxicity (rat)
- ◆ NOAEL at 517 mg/kg-d
- ◆ Total UF=100 (UFh=10; UFa=3; UFd=3; UFc=1; UFl=1)
- ◆ Oral RfD = 5.2 mg/kg-d to protect *in utero* exposure

RfC Derivation for p-Dioxane

- ◆ Key Study
 - Torkelson *et al.* 1974
- ◆ Key Effects
 - No effects seen at 111ppm (rats)
- ◆ NOAEL at 111 ppm (or 108 mg/kg-d)
- ◆ Total UF=100 (UFh=10; UFa=3; UFd=3; UFc=1; UFl=1)
- ◆ Inhalation RfC = * 1.1 mg/kg-d

* As discussed in Section 7.2 of the meeting report, the RfC value of 1.1 mg/kg-d presented in this slide (“RfC Derivation for p-Dioxane”) is wrong because the correction factor of 5/7 to account for inhalation exposure duration was not included in its calculation. The correct RfC value is 0.72 mg/kg-d.

Quantitation of Hazard

- ♦ Hazard Index (HI) approach used for cancer and non-cancer endpoints
- ♦ Total HIs less than or equal to 1 not considered a hazard

VCCEP Total Hazard Indices For Most Highly Exposed Child

Population Category	Exposure Category	Total HI
Infant (0-1 years)	Central Tendency	0.4
	Upper Bound	1

Indicates that even the most highly exposed child is not at risk from these p-dioxane exposures

VCCEP Total HIs For Most Highly Exposed Pregnant Worker

Population Category	Exposure Category	Total HI
Pregnant Worker (fetus)	Central Tendency	0.2
	Upper Bound	0.5

Indicates that even the most highly exposed pregnant worker is not at risk from these p-dioxane exposures

Summary

- ♦ Animal toxicity observed > 10 mg/kg-d for non-cancer effects and > 40 mg/kg-d for liver tumors
- ♦ Child HI range = 0.1 – 1
- ♦ Pregnant worker HI range = 0.2 – 0.5
- ♦ The most highly exposed child and prospective parent do not appear to be at risk from these p-dioxane exposures

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VCCEP Peer Consultation: Data Gaps/Needs for p-Dioxane

Richard P. Hubner, M.P.H.
The Sapphire Group

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Michael L. Gargas, Ph.D.
The Sapphire Group

2 May 2007



Data Gaps/Needs Overview

- ♦ Toxicity
- ♦ Dose-Response
- ♦ Exposure Assessment
 - Occupational
 - Water
 - Air
 - Food and Consumer Products
- ♦ Conclusions

Toxicity Data Gaps/Needs

- ♦ Immunotoxicity Study
 - Currently no specific p-Dioxane study
 - No histopathology or clinical biochemical immune response in current studies
 - No increase in infectious disease in current studies
 - No damage to immune system in current studies
 - No sensitization potential
- ♦ Therefore, immunotoxicity study may not be necessary

Toxicity Data Gaps/Needs

- ♦ Neurotoxicity
 - Currently no specific p-Dioxane study
 - High-dose exposure elicit the same non-specific, reversible neurotoxicity observed with other solvents
 - No neurotoxicity has been observed in humans or laboratory animals at lower doses
 - No evidence from gross pathology or histopathology that the nervous system is a target organ for p-Dioxane
- ♦ Therefore, neurotoxicity study may not be necessary

Toxicity Data Gaps/Needs

- ♦ Developmental Neurotoxicity
 - Currently no specific p-Dioxane study
 - Current studies indicate that p-Dioxane is not a significant reproductive or developmental toxicant
 - Doses likely experienced by exposed fetuses are well below reference doses, which are protective against critical endpoints
- ♦ Therefore, developmental neurotoxicity study may not be necessary

Hazard Assessment Data Gaps/Needs

- ♦ DATA GAP/NEED: potential refinement under Hill Criteria and IPCS for human relevance.

Exposure Assessment Data Gaps/Needs

- ◆ Occupational
 - DATA GAP/NEED: Improved workplace exposure data
- ◆ Water
 - DATA GAP/NEED: USEPA may wish to survey water systems affected by chlorinated solvent contamination to assess the potential problem.
- ◆ Air
 - DATA GAP/NEED: TEAM studies may need to be re-visited and expanded to assess current exposure to p-Dioxane and other contaminants of concern.
- ◆ Food and Consumer Products
 - DATA GAP/NEED: USEPA and/or FDA may wish to survey to identify and quantify all consumer products and foods which may contain p-Dioxane.

Conclusions

- ◆ Toxicologic Data Gaps/Needs are of low priority.
- ◆ Potential refinement under Hill Criteria and IPCS for human relevance.
- ◆ Exposure data are dated and need improvement.

Appendix D
Voluntary Children's Chemical Evaluation Program (VCCEP)
Peer Consultations on P-Dioxane

May 1-2, 2007

Additional Handouts and Presentations from the Panel Discussions

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Additional Handouts and Presentations from the Panel Discussions

- Two tables prepared by the sponsor during the meeting from the submission's Appendix A. These tables show concentrations of p-dioxane in breast milk are higher than in formula reconstituted with tap water
- *Interspecies Extrapolation for Non-Cancer Risk Assessment*: eight slides presented by a panel member during the meeting
- *Internal Doses of Trihalomethanes in Humans Resulting from Drinking Water Use*: 25 slides presented by a panel member during the meeting
- Sweeney, L.M. and Gargus, M.L. 2006. Physiologically-based pharmacokinetic (PBPK) modeling of 1,4-dioxane in rats, mice, and humans. Prepared by The Sapphire Group, Dayton, Ohio, for ARCADIS, Southfield, Michigan, on behalf of the Dioxane Risk Management Consortium, October 18, 2006. **NOTE:** The document in this appendix is the report as it was presented to the panel during the VCCEP peer consultation meeting on May 1-2, 2007. Subsequent to the panel meeting, the report has been submitted for publication and has been accepted pending revision.

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Infant tap

Media	ADD (mg/mk - day)			LADD (mg/mk-day)		
	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal
Water	1.4E-04		6.4E-09	1.9E-06		9.2E-11
Lotion			3.8E-04			5.4E-06
Air		1.5E-04			2.2E-06	
Food	7.7E-04			1.1E-05		
Route Subtotal	9.1E-04	1.5E-04	3.8E-04	1.3E-05	2.2E-06	5.4E-06
Total	1.4E-03			2.1E-05		

Media Concentrations	Water (mg/L)	Cw	0.002
	Lotion (mg/L)	Cl	10
	Ambient Air (mg/m3)	Caa	0.00026
	Food (mg/mk)	Cf	0.005

General Parameters	Population name	Child				
	Body Weight (kg)	BW	7.4	4.8	11.2	CEFH, 2006
	Averaging Time, noncancer (d)	ATn	365			
	Averaging Time, cancer (d)	ATc	25550			
	Exposure Time (hr)	ET	24			
	Exposure Time for Bathing (hr)	ETb	0.17			
	Exposure frequency (d/y)	EF	365			
	Exposure duration (y)	ED	1			

Intakes	Groundwater ingestion (L/d)	IW	0.5	0.25	1.3	
	Groundwater reduction factor (unitless)	AFw	1			
	Food (mg/d)	IF	1143300			
	Food reduction factor (unitless)	Aff	1			
	Inhalation rate (m3/d)	IA	8.6	4.6	12.7	CEFH, 2006
	Inhalation reduction factor (unitless)	Afa	0.5			
	Total skin surface area (cm2)	SA	3256			Calculated fom body weight using conversion (380 cm2/kg)
	Total skin reduction factor (unitless)	AF	1			obtained from CEFH, 1999
	Lotion Skin fraction	Fl	1			
	Lotion skin fraction adjustment factor	AFI	0.083	0	0.25	adjusted for ET (0,0.25, 0.5 hrs) less than 24 hours
Chemical-Specific	Permeability Coefficient (cm/hr)	Kp	0.000043			

Food intakes (g/kg-day) (CEFH, 2006)		
154.5	77.3	322.6

This table was prepared by the sponsor during the p-Dioxane meeting from information in the submissions Appendix A.

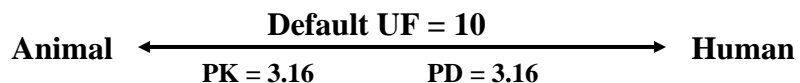
Children (1-2 years)	Oral Dose (mg/kg-day)			Note - These sample calculations do not consider variation from terms other than dioxane source. Relative contribution of water to total oral dose changes at the tails vs. at the most likely estimate.
	Using Minimum of Source Triangular Distribution (sample calculation)	Using Most Likely of Source Triangular Distribution (from p. A-30)	Using Maximum of Source Triangular Distribution (sample calculation)	
water	1.3E-05	5. 4E-05	5.4E-02	
food	0.0E+00	3.8E-04	3.8E-02	
total	1.3E-05	4.4E-04	9.2E-02	
Relative Contribution of Water to Total Oral Dose	100%	12%	58%	
results from Table 6-7 (p-150)	mean	95th Percentile	Comparison of the max source values above are slightly higher than the 95th percentile (as expected). Therefore, the MC results in Table 6-7 accurately reflect the triangular distribution assumptions used for dioxane in water and food.	
	2.6E-02	6.8E-02		

This table was prepared by the sponsor during the p-Dioxane meeting from information in the submissions Appendix A.

Interspecies Extrapolation for Non-Cancer Risk Assessment

John C. Lipscomb, PhD, DABT
US EPA, Office of Research and Development
National Center for Environmental Assessment
26 W. ML King Drive, MC-A-110
Cincinnati, Ohio 45268
T 513.569.7217
F 513 487.2539
Lipscomb.john@epa.gov

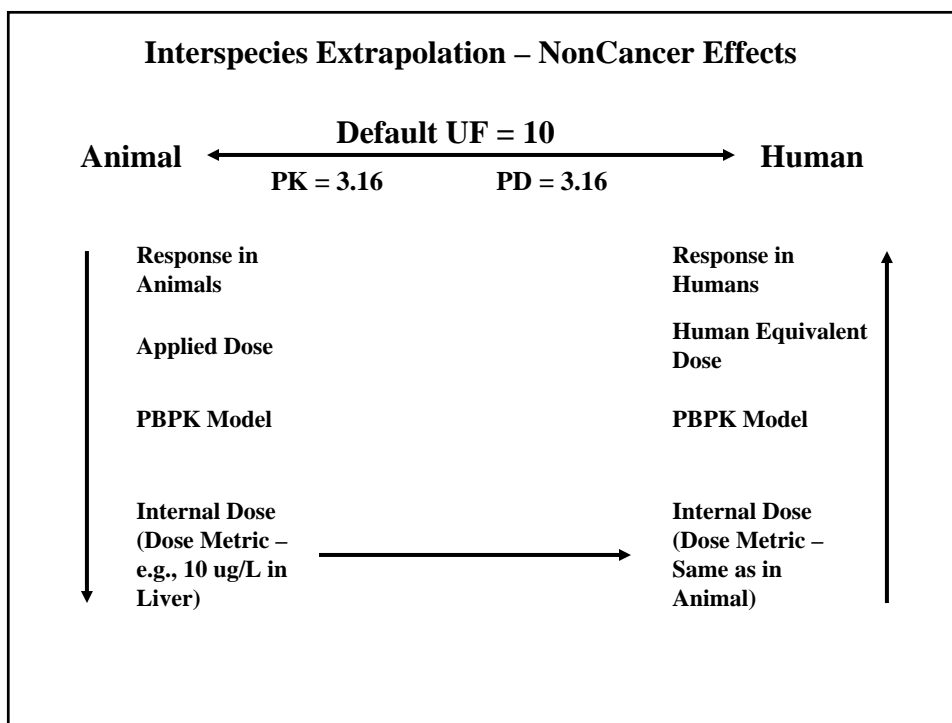
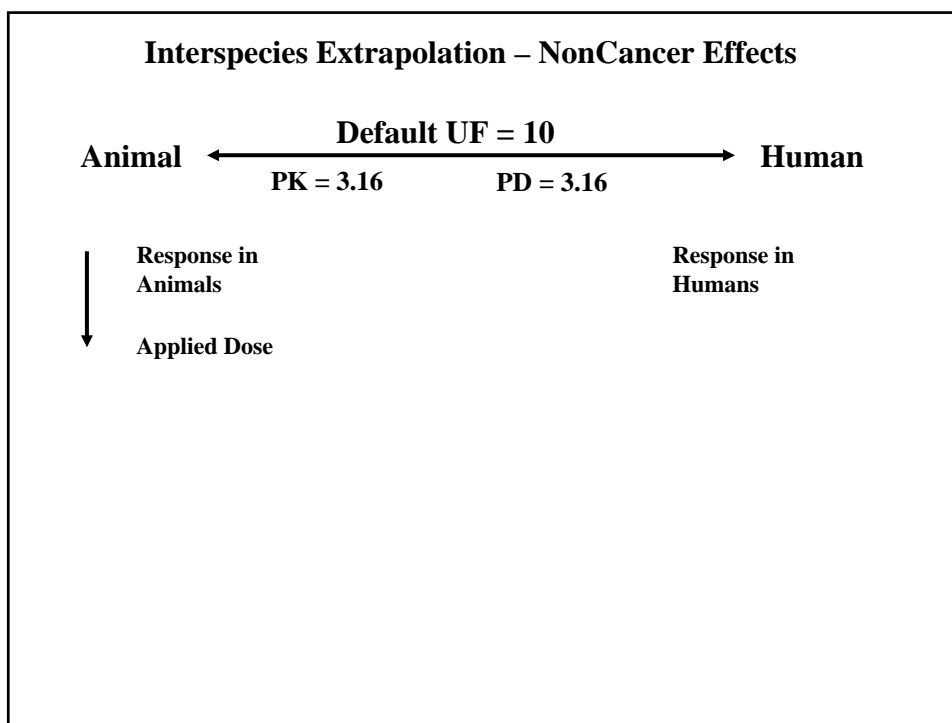
Interspecies Extrapolation – NonCancer Effects



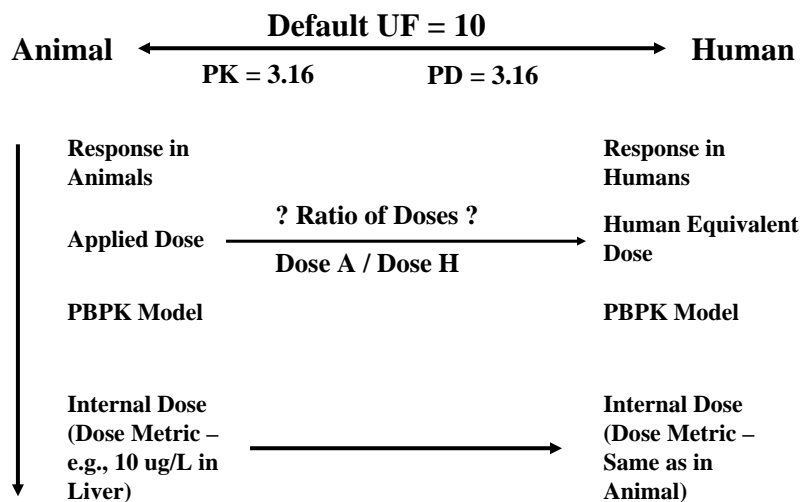
**With confidence in toxicity data
and with an adequate Pharmacokinetic
description (model), the default value
of 3.16 can be replaced.**

Do we have that data and sufficient confidence?

What would the new value be?



Interspecies Extrapolation – NonCancer Effects



Confidence?

Some issues include:

- **Model Structure**
- **Model Parameter Values – newly derived**
- **Fit to Data? - Problematic**
- **Modifications to Model –**
 - Metabolic induction?** Timing, magnitude
 - Consider short studies in vivo
 - Renal elimination?** Acid metabolite in urine
 - Consider modification to renal acid pump
 - Others?**

Internal Doses of Trihalomethanes in Humans Resulting from Drinking Water Use

John C. Lipscomb, PhD, DABT
US EPA, Office of Research and Development
National Center for Environmental Assessment
Cincinnati, Ohio

Charles R. Wilkes
Wilkes Technologies, Inc
Bethesda, Maryland

Gregory L. Kedderis
Independent Consultant
Chapel Hill, North Carolina

Moving Toward Cumulative Risk Assessment
Joint SETAC/SRA Meeting, Argonne National Laboratory
Argonne, Illinois

Friday, March 16, 2007

The Issue

Drinking Water
Internal Doses
Residential Applications
Multi-Route Application
Probabilistic Approach
Trihalomethanes
Toxicity – basis and effects

**How would internal doses of THMs from a Multi-Route
in-home exposure compare to internal doses
attained at Agency Reference values?**

**Would toxicologic interactions among these
THMs be expected?**

The Approach

The Water

The House

Human Activity

Exposures and Doses:

Total Exposure Modeling (TEM; Wilkes Technologies)

Physiologically Based Pharmacokinetic (PBPK) Modeling

Results and report peer reviewed, available on the web

The Water

US EPA, Information Collection Rule

N = 330 utilities; July 1997 – December, 1998

Concentration of DBPs varied

source water, season, location, treatment type

For THMs, Cl \longleftrightarrow Br: negative correlation

THM Concentrations Employed

Variable Subgroup	THM Analysis Description	Concentration, ppb (Percentile)			
		Chloroform	BDCM	DBCM	Bromoform
All Systems Using Surface Water Intake (N = 12,440)	Chloroform 95th Percentile	66.0 (95)	29.0 (98)	12.0 (90)	0.5 (0)
	BDCM 95th Percentile	26.1 (62)	23.8 (95)	17.7 (95)	2.6 (89)
	DBCM 95th Percentile	140.0 (100)	44.0 (100)	17.0 (95)	3.7 (92)
	Bromoform 95th Percentile	14.0 (34)	25.0 (96)	26.0 (98)	5.6 (95)

The House

Building Characteristics -

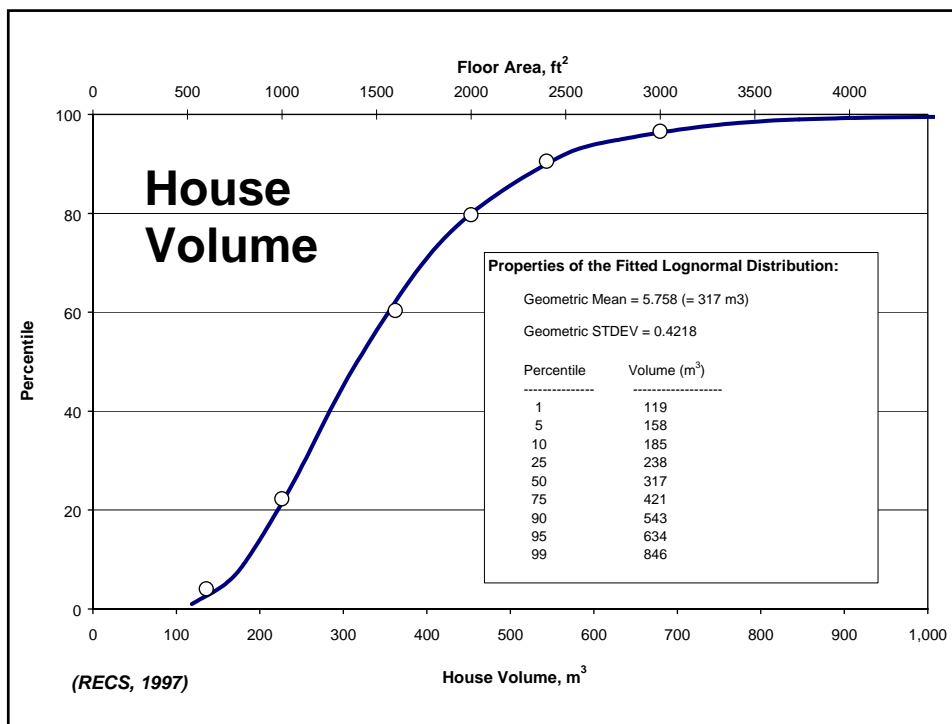
Household volumes - US EPA, EFH; RECS

Air Exchange rates – US EPA, EFH; NIST

Appliances (e.g., shower): US HUD, frequency, duration, temperature

Volatilization models: plug-flow model, completely mixed flow model

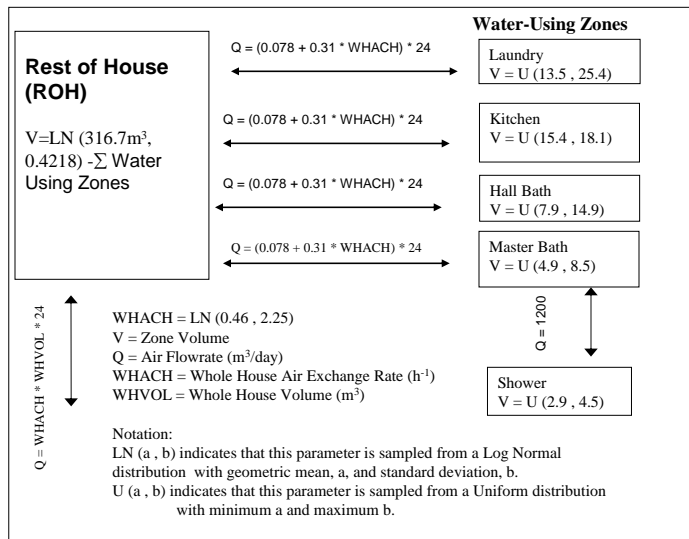
Mass Transfer Coefficient – fn of appliance, temperature, flow rate



Estimated Dimensions of Water-Use Zones			
Zone	Dimension	Small	Large
Hall Bath	Area (m ²)	3.2	6.1
	Volume (m ³)	7.9	14.9
Master Bath	Area (m ²)	2.0	3.5
	Volume (m ³)	4.9	8.5
Kitchen	Area (m ²)	6.3	7.4
	Volume (m ³)	15.4	18.1
Laundry	Area (m ²)	5.5	10.4
	Volume (m ³)	13.5	25.4
Shower	Area (m ²)	1.2	1.8
	Volume (m ³)	2.9	4.5

(Hoke 1988, 1994)

Schematic Representation of House Interzonal Air Flows



Water Using Appliances

Toilet
 Faucets
 Shower
 Bath
 Clothes Washer
 Dishwasher

Human Activity

Water Use Patterns –

NHAPS (US EPA/ORD/NERL): water use activities and locations

REUWS (AWWA): household water flow rates at meter & disaggregated

RECS (source): building characteristics & energy consumption

Ingestion: US EPA, 2000, CSFII

Appliance Manufacturer Data

Human Activity

Human Behavior Characteristics – NHAPS

N = 9386, October, 1992 – September, 1994

24 hour recall:

91 potential activities

food cleanup, bathing/showering, plant care, personal care ...

83 potential locations

home – bedroom, home-kitchen, home – bathroom, office, transit ...

Selected Model Parameters for Showers	
Statistic	Value
Shower Frequency per person per day	
Children 6 years	0.6
Men 15-45 years	1.2
Women 15-45 years	1.1
Shower Duration (Geometric Mean)	6.8 minutes
Shower Duration (Geometric Standard Deviation)	1.64 minutes
Shower Flowrate	2.4 gallons/minute

Water-Use Activity Pattern from NHAPS Database for Simulation Number 48.

Source Name	Model Location	Occupant	Time On, hours	Time Off, hours	Duration, min
Toilet	Master Bathroom	Male	5.511	5.537	1.6
Faucet -- Kitchen	Kitchen	Child	8.365	8.372	0.4
Toilet	Master Bathroom	Female	9.594	9.630	2.1
Faucet -- Kitchen	Kitchen	Female	10.271	10.279	0.5
Dishwasher	Kitchen	Female	10.279	11.527	74.9
Shower	Master Bathroom	Female	17.004	17.122	7.1
Faucet -- Kitchen	Kitchen	Male	18.063	18.064	0.1
Faucet -- Laundry	Laundry	Child	19.449	19.461	0.7
Hall Bath	Hall Bath	Child	19.25	19.703	27.2
Hall Toilet	Hall Bath	Child	19.663	19.680	1.1

WATERUSES: (Indicates when each appliance is in use)

Appliance	Start Time (hours)	End Time (hours)
Dishwasher	9.5	11.5
Faucet-M Bathroom	5.5	5.5
Faucet-Kitchen	8.5	8.5
Faucet-Laundry	10.5	10.5
Bath-Hall Bathroom	17.5	17.5
Toilet-Hall Bathroom	19.5	19.5
Shower-M Bathroom	17.5	17.5
Toilet-M Bathroom	5.5	5.5

Air Concentration, $\mu\text{g/L}$

Time, hours

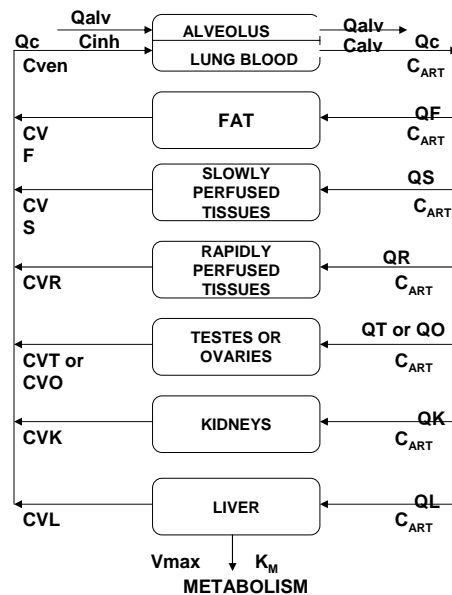
Legend:

- Female, Chloroform, Personal Concentration (Red solid line)
- Female, DBCM, Personal Concentration (Blue solid line)
- Female, DBCM, Personal Concentration (Black solid line)
- Female, Bromoform, Personal Concentration (Purple dashed line)

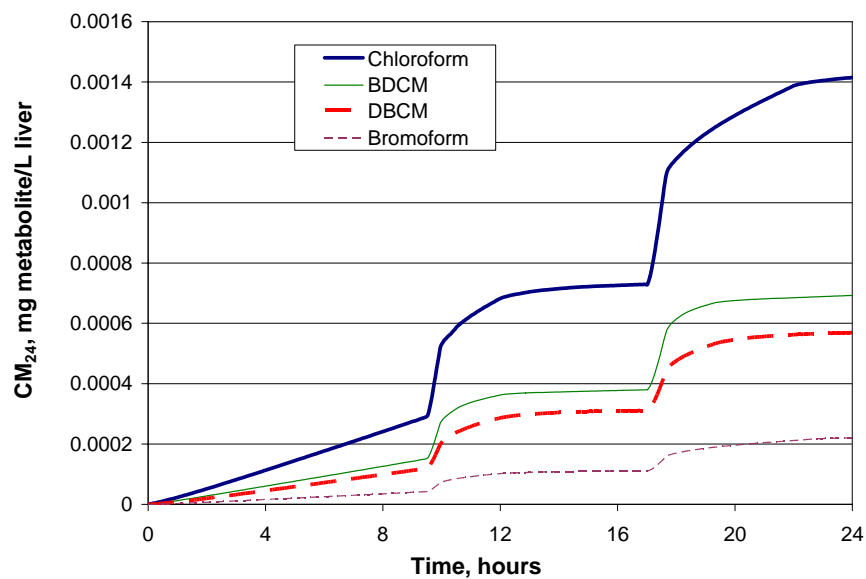
The graph shows two major peaks in air concentration around 9.5-10 hours and 17.5 hours. The first peak is dominated by Chloroform (red line) reaching approximately 0.85 $\mu\text{g/L}$. The second peak is also dominated by Chloroform, reaching approximately 1.0 $\mu\text{g/L}$. DBCM (blue and black lines) shows smaller peaks at the same times, reaching approximately 0.25 $\mu\text{g/L}$ and 0.35 $\mu\text{g/L}$ respectively. Bromoform (purple dashed line) remains near zero throughout the 24-hour period.

Toxicity through metabolites

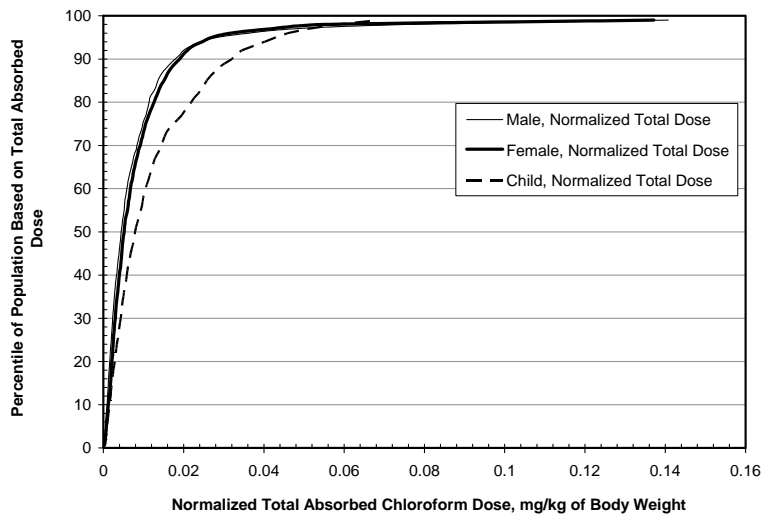
Physiologically Based Pharmacokinetic Model Structure



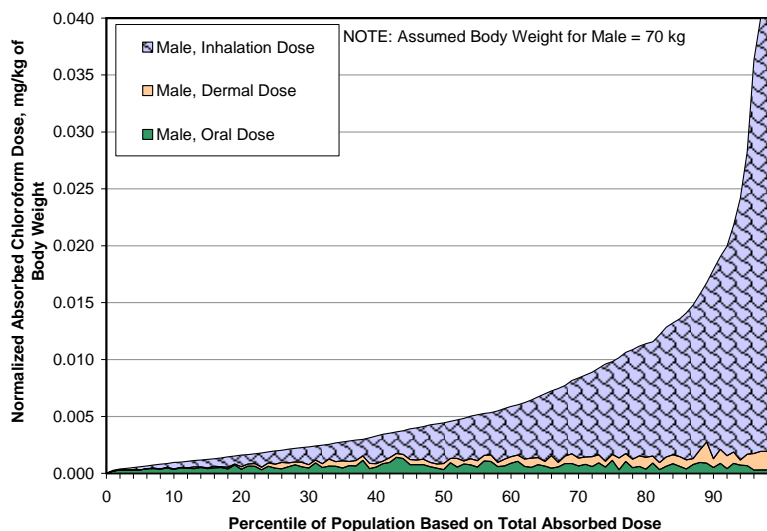
PBPK Simulation of Internal Dose Metric for THMs in Liver



Population Distribution of Absorbed Chloroform Dose



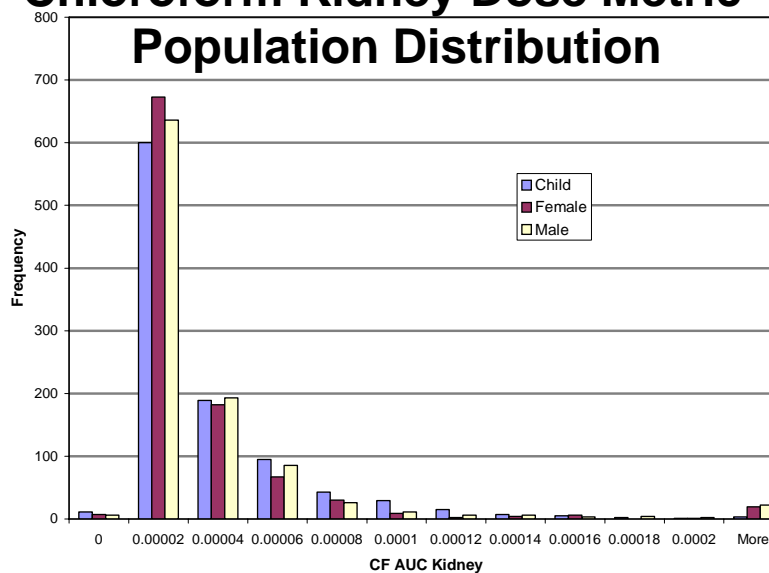
Exposure Route Contributions to Chloroform Absorbed Dose



Total Absorbed Dose, mg/kg

	Chloroform	BDCM	CDBM	Bromoform
Female				
0.05	7.6 E-4	2.8 E-4	2.1 E-4	6.5 E-5
0.50	5.1 E-3	1.7 E-3	1.1 E-3	3.3 E-4
0.95	2.8 E-2	8.7 E-3	5.6 E-3	1.5 E-3
Male				
0.05	5.9 E-4	2.1 E-4	1.6 E-4	5.3 E-5
0.50	4.4 E-3	1.4 E-3	9.9 E-4	3.0 E-4
0.95	2.9 E-2	9.4 E-3	2.0 E-3	1.7 E-3
Child				
0.05	9.2 E-4	4.1 E-4	2.5 E-4	8.8 E-5
0.50	7.9 E-3	2.6 E-3	1.7 E-3	4.9 E-4
0.95	4.3 E-2	1.4 E-2	8.7 E-3	2.4 E-3

Chloroform Kidney Dose Metric - Population Distribution



Metabolic Inhibition?

No.

How About with Decreased Amount of Enzyme?

Still, No.

**Well, Maybe – but at 6 orders of magnitude
lower enzyme, less than 20% inhibition.**

Conclusions

- **The strongest correlations were found with:
Shower, bath duration
Time spent in the bathroom
The fraction of time spent in the home multiplied
by the total volume of water use in the home**
- **Total doses do not raise concerns when
compared to oral RfD values.**
- **Metabolic inhibition and altered pharmacokinetics and
mixtures risks seem uncomplicated by
these exposure conditions**

Citation:

U.S. EPA. 2006. Exposures and Internal Doses of Trihalomethanes in Humans: Multi-Route Contributions from Drinking Water. Office of Research and Development, National Center for Environmental Assessment, Cincinnati, OH. EPA/R-06/087.

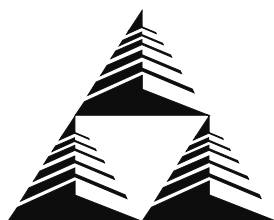
<http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=153303>

Supported by a Contract to Wilkes Technologies, Inc, Bethesda, MD.

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Physiologically-based Pharmacokinetic (PBPK) Modeling of 1,4-Dioxane in Rats, Mice and Humans

Final Report



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For

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On Behalf of the Dioxane Risk Management Consortium

October 18, 2006

Executive Summary

1,4-Dioxane (CAS No. 123-91-1) is used primarily as a solvent or as a stabilizer for solvents. 1,4-Dioxane has been shown to produce liver and nasal tumors in rodents, but the relevance of the nasal tumors is uncertain. Two physiologically-based pharmacokinetic (PBPK) models for 1,4-dioxane and its major metabolite, hydroxyethoxyacetic acid (HEAA), were published in 1990 (Reitz *et al.*, 1990; Leung and Paustenbach, 1990) and were used to derive cancer potency estimates for 1,4-dioxane. Since 1990, new data have been collected for model parameterization and validation. Updated models that incorporate our improved understanding of the uptake, distribution, metabolism, and elimination of 1,4-dioxane and HEAA were developed based on this new data. These models will serve as better tools for uncertainty reduction in future 1,4-dioxane risk assessments.

INTRODUCTION

1,4-Dioxane (CAS No. 123-91-1) is used primarily as a solvent or as a stabilizer for solvents. 1,4-Dioxane has been shown to produce liver and nasal tumors in rodents, but the relevance of the nasal tumors is uncertain (see summary by Stickney et al., 2003). Two physiologically-based pharmacokinetic (PBPK) models for 1,4-dioxane and its major metabolite, hydroxyethoxyacetic acid (HEAA), were published in 1990 (Reitz *et al.*, 1990; Leung and Paustenbach, 1990) and were used to derive improved cancer potency estimates for 1,4-dioxane. These improved potencies were many orders of magnitude less potent than those derived by the USEPA during their last evaluation of 1,4-dioxane carcinogenicity in 1990 using standard default approaches.

The Sapphire Group (2005) previously reviewed the existing 1,4-dioxane PBPK models and made recommendations for filling “data gaps” pertaining to the pharmacokinetics of 1,4-dioxane and HEAA in rats, mice, and humans. Subsequently, studies were performed at Battelle Pacific Northwest Laboratory for the purpose of filling these data gaps (Thrall et al., 2005; Poet et al., 2005, 2006). Three types of studies were performed: partition coefficient measurements, blood time course in mice, and *in vitro* pharmacokinetics. The partition coefficient measurements consisted of new measurements for mouse blood and tissues (liver, kidney, fat, and muscle) and confirmatory measurements for human blood and rat blood and muscle. The blood time course measurements in mice were conducted for gavage administration of nominal single doses (20, 200, or 2000 mg/kg) of 1,4-dioxane administered in water. Vial incubations of 1,4-dioxane with rat liver microsomes failed to produce detectable declines in headspace concentration of 1,4-dioxane or increases in HEAA in buffer. Incubations of 1,4-dioxane with rat and mouse hepatocytes did produce measurable amounts of HEAA, and estimates of rate constants for metabolism of 1,4-dioxane by rat and mouse liver were thus derived.

In the present effort, we have developed PBPK models for the rat, mouse, and human which are consistent with the newly collected data (described above) and previous kinetic studies in rats and human volunteers reported by Young et al. (1977, 1978).

METHODS

Source Data

Mouse pharmacokinetic data were provided in spreadsheet form by Dr. Karla Thrall of Battelle. Some human and rat pharmacokinetic data were available in numerical form from Dr. Dick Reitz (retired, Dow Chemical) and from Young et al. (1976). Additional human and rat pharmacokinetic data were available in graphical form from Young et al. (1977, 1978). Scanned images were converted into numerical data using Plot Digitizer (version

2.4.0), with minor adjustments made to match reported sampling times. Copies of worksheets reporting blood 1,4-dioxane and HEAA concentrations for the four individuals in Young et al. (1977) were graciously provided by Dr. Bill Stott, Dow Chemical Company, Midland, Michigan. A copy of the unpublished detail is included as Appendix A.

Model Description

The model structure was similar to those used by Reitz et al. (1990) and Leung and Paustenbach (1990) and is depicted in **Figure 1**. Model parameter values are summarized in **Table 1**. Tissue volumes and fractional blood flow rates were taken from Brown et al. (1997). Partition coefficients were generally taken from Thrall et al. (2005). The measured mouse kidney:air partition coefficient used for all three species, and muscle:air partition coefficients used for slowly perfused tissues. The rat fat:air value was reported by Reitz et al. (1990). Human liver:air, fat:air and slowly perfused tissue:air partition coefficients were estimated as the average of measured mouse and rat values.

Table 1. PBPK Model Parameter Values for 1,4-Dioxane

Parameter	Units	Rat	Mouse	Human	Source/Comments
Body weight (BW)	kg	0.25	0.025	70	Default; experiment- specific values used when available
Fractional volume of liver (VLC)	(none)	0.034	0.055	0.033	Brown et al. (1997)
Fractional volume of adipose (VFC)	(none)	0.07	0.07	0.214	Brown et al. (1997)
Fractional volume of richly perfused tissues (VRC)	(none)				$VRC = 1 - (VLC + VFC + VSC + VBC + VUC)$
Fractional volume of slowly perfused tissues (VSC)	(none)	0.594	0.549	0.437	Brown et al. (1997)
Fractional volume of blood (VBC)	(none)	0.074	0.049	0.079	Brown et al. (1997)

Parameter	Units	Rat	Mouse	Human	Source/Comments
Fraction of unperfused tissue (VUC)	(none)	0.05	0.054	0.071	Brown et al. (1997)
Normalized alveolar ventilation rate (QPC)	L/hr-kg ^{0.74}	13	20	13	Brown et al. (1997)
Normalized cardiac output (QPC)	L/hr-kg ^{0.74}	13	20	13	Brown et al. (1997)
Fractional blood flow to liver (QLC)	(none)	0.183	0.161	0.227	Brown et al. (1997)
Fractional blood flow to adipose (QFC)	(none)	0.07	0.07	0.052	Brown et al. (1997)
Fractional blood flow to richly perfused tissues (QRC)	(none)				1 - (QLC + QFC + QSC)
Fractional blood flow to slowly perfused tissues (QSC)	(none)	0.336	0.217	0.249	Brown et al. (1997)
Blood/air partition coefficient (PB)	(none)	1861	2002	1666	Thrall et al. (2005)
Liver/air partition coefficient (PLA)	(none)	1862	1143	1500	Rat and mouse: Thrall et al. (2005); human: average of rat and mouse
Adipose/air partition coefficient (PFA)	(none)	851	879	865	Rat: Reitz et al. (1990); mouse: Thrall et al. (2005); human: average of rat and mouse

Parameter	Units	Rat	Mouse	Human	Source/Comments
Richly perfused tissues/air partition coefficient (PRA)	(none)	560	560	560	Mouse kidney, Thrall et al. (2005); rat and human: assumed equal to mouse kidney
Slowly perfused tissues/air partition coefficient (PSA)	(none)	1348	1705	1503	Rat and mouse: Thrall et al. (2005); human: average of rat and mouse
Normalized Maximal rate of metabolism of 1,4-dioxane in liver (VmaxC)	mg/hr-kg ^{0.7}	7.5 or 12.7	39 or 46	54 to 192	Rat (uninduced/induced) and mouse: optimized fit to <i>in vivo</i> data; human: parallelogram approach, based on scaled <i>in vitro</i> data
Michaelis constant for metabolism of 1,4-dioxane in liver (Km)	mg/L	21	21	29 to 147	Rat: optimized fit to <i>in vivo</i> data. Mouse: equality to rat assumed, based on <i>in vitro</i> data; human: scaled from rat <i>in vivo</i> Km using <i>in vitro</i> human:rat ratios
Normalized volume of distribution for metabolite (VDMC)	L/kg	1	0.83	0.83	VDMC not identifiable for rat; value of 1 assumed; mouse: optimized, human: equality to mouse assumed

Parameter	Units	Rat	Mouse	Human	Source/Comments
Elimination rate of metabolite (Kme)	hr ⁻¹	0.48	0.35	0.35	Rat and mouse: optimized based on fit to <i>in vivo</i> data, human: equality to mouse assumed

Estimated/Optimized Parameters

The determination of certain model parameters by estimation/optimization is described in greater detail under “Results”, but described briefly below.

The metabolic rate constants VmaxC (maximum rate of metabolism, normalized to scaled body weight, BW^{0.7}) and Km (Michaelis constant, or apparent enzyme affinity) for rats were derived by fit to the intravenous (iv) data of Young et al. (1978). Young et al. (1978) had noted that administration of a dose of 1000 mg/kg, but not 10 mg/kg 1,4-dioxane appeared to induce metabolism of 1,4-dioxane. Nannelli et al. (2005) also reported the induction of cytochrome P450 2B1/2- and 2E1-dependent metabolic activities in rat liver due to oral exposure to 1,4-dioxane. The appropriateness of dose-specific VmaxC values was tested by optimizing the fit to high or low iv doses separately.

The first-order rate parameter for urinary elimination of HEAA by rats was determined by optimizing the fit to urinary excretion data for iv and oral dosing (Young et al., 1978).

Based on the similarity of Km values derived *in vitro* for metabolism of 1,4-dioxane by rats, mice, and humans, (Poet et al., 2005, 2006), the Km value derived by optimization for rats was also used for the other species. Estimates of the oral absorption rate constant and VmaxC values for mice were made based on fit to blood 1,4-dioxane concentrations reported by Thrall et al. (2005). Because the analytical method measured background/artifactual levels of 1,4-dioxane and HEAA levels in blood of unexposed mice, only values that were >3-fold higher than the background level were used in modeling. The oral absorption rate constant for mice was also applied to simulations of oral dosing in rats.

Human VmaxC estimates were made using the parallelogram approach, relying on the “best fit” *in vivo* values derived for rats and mice and the *in vitro* rates determined using rat, mouse, and human hepatocytes (Poet et al., 2005, 2006). Hepatocyte yields of 128, 110, or 137 × 10⁶ hepatocytes per gram of mouse, rat, and human liver (Seglen, 1978, Arias et al.,

1982, and Carlile et al., 1997), respectively, and the default tissue volumes and body weights in Table 1 were used to scale *in vitro* data.

The first order elimination rate for metabolite in urine (K_{me}) of rats was estimated by best fit to amounts excreted when rats were dosed by single iv or gavage (Young et al., 1978). K_{me} and the volume of distribution of the metabolite (VDMC) of mice was estimated by best fit to blood concentrations of HEAA measured in mice dosed by gavage (Thrall et al., 2005).

Model Validation

The model was further tested against additional data of Young et al. (1976, 1977, 1978) and Thrall et al. (2005) as described under “Results.”

Software and Algorithms

All simulations and parameter fitting were conducted using ACSL Sim 11.4 and ACSL Math, Version 2.5.4 (Aegis Technologies, Hunstville, Alabama) on a Dell Optiplex GX260 computer with a Pentium 4 processor. The Gear algorithm was used for integration of double precision variables. Parameter fitting was performed using the relative error model (variance is assumed to be proportional to the measured value across the range of measured values, or heteroscedasticity = 2) and the Nelder-Mead algorithm. The fitting criterion was maximization of the log likelihood function. Starting values for parameter fitting in ACSL Math were determined from parameter estimates derived by visual best fit in ACSL Sim. Goodness of fit is described as the “percentage of variation explained”, which is similar to the r^2 value derived for linear regression.

RESULTS

Determination of V_{maxC} and K_m for the Rat

Preliminary values of V_{maxC} and K_m in the rat were derived by optimizing the fit to the 1000 mg/kg iv data (Young et al., 1978) (“induced” rat V_{maxC}) and iv doses of 3, 10, 30, and 100 mg/kg (“uninduced” rat V_{maxC}). The 300 mg/kg iv data were initially omitted as a likely border-line case which could distort the optimization of fit to “high” and “low” data. Preliminary best-fit values of $V_{maxC} = 12.8 \pm 0.036$ mg/hr-kg^{0.7} and $K_m = 22.0 \pm 1$ mg/L were derived for the induced rat, and values of $V_{maxC} = 7.4 \pm 0.05$ mg/hr-kg^{0.7} and $K_m = 20.5 \pm 1.4$ mg/L for the uninduced rat. Because of the similarity of the K_m s for the uninduced and induced rats, an average value of $K_m = 21$ mg/L was selected as being applicable to all doses. With the K_m value set at 21 mg/L, the best-fit value of V_{maxC} for induced rats, 12.7 ± 0.08 mg/hr-kg^{0.7} (80.4% of variation explained) was determined from fit of the 1000 mg/kg data. Likewise, a best fit value of $V_{maxC} = 7.5 \pm 0.2$ mg/hr-kg^{0.7} was derived for uninduced rats (66.6 % of variation explained). The best-fit V_{maxC} for the 300

mg/kg iv data was found to be $10.8 \pm 0.2 \text{ mg/hr-kg}^{0.7}$, indicating that these data would be more appropriately described by the “induced” VmaxC rather than the uninduced VmaxC. The model fit to the iv data is shown in **Figure 2**.

Determination of VmaxC, Km, and KA for the Mouse

The *in vivo* Km value for the mouse was estimated as being equal to the best-fit rat value of 21 mg/L. The basis for this selection was that the *in vitro* Kms for production of HEAA from 1,4 dioxane from incubated rat and mouse hepatocytes (2.51 ± 0.88 and 2.63 ± 0.68 mg/ml) are statistically indistinguishable. Thus it is expected that the *in vivo* Kms will also be similar. The *in vivo* mouse data (Thrall et al., 2005) have insufficient samples where the blood concentration of 1,4-dioxane was at or below the likely Km, so it was not possible to identify the *in vivo* Km on the basis of fit to the *in vivo* data.

Mouse VmaxC and KA values were derived by optimizing fit to the blood 1,4-dioxane concentrations in mice administered nominal doses of 200 and 2000 mg/kg 1,4-dioxane by gavage in a water vehicle. 1,4-Dioxane measurements in blood of the animals in the 20 mg/kg group were indistinguishable from the background for the analytical method, and thus could not be used for pharmacokinetic analysis. Because doses >300 mg/kg have been found to induce 1,4-dioxane metabolism in rats, the possibility of dose-dependency of VmaxC was also assumed for mice. Preliminary VmaxC and KA values for potentially induced mice (2000 mg/kg dose) were $46.6 \pm 1.1 \text{ mg/hr-kg}^{0.7}$ and $0.73 \pm 0.09/\text{hr}$, while the preliminary values for uninduced mice (200 mg/kg) were $39.1 \pm 0.3 \text{ mg/hr-kg}^{0.7}$ and $0.94 \pm 0.009/\text{hr}$. Because the absorption rate would be expected to be similar across doses, a single value of 0.8/hr was assumed for both doses. With KA fixed, dose-dependent VmaxC values were then optimized as 46 ± 1 and $39 \pm 1 \text{ mg/hr-kg}^{0.7}$ for 2000 mg/kg and 200 mg/kg mice, respectively (91.8 and 91.5 % of variation explained, respectively). The model fit to the mouse oral data is shown in **Figure 3**.

Scaling of *in vitro* Metabolism Data/Estimation of Human VmaxC and Km

The *in vitro* Vmax values for rats and mice (Poet et al., 2005) were scaled to estimated *in vivo* rates, which were compared to the optimized values. The scaled and optimized rat VmaxCs were very similar. The discrepancy between the scaled and optimized mouse values was larger, which was attributed to possible induction in mice at the lowest dose tested (200 mg/kg). The ratio of optimized/scaled values for the rat was used to adjust the scaled human VmaxC values to projected *in vivo* values.

Table 2. Scaling of 1,4-Dioxane Metabolism in Hepatocytes

	<i>In vitro</i> rate ($\mu\text{g/hr} \cdot 10^6$ cells) ^a	Scaled rate (mg/hr- $\text{kg}^{0.7}$)	Optimized <i>in</i> <i>vivo</i> rate (mg/hr- $\text{kg}^{0.7}$) ^b	Ratio of <i>in</i> <i>vivo</i> /scaled rates	Estimated <i>in vivo</i> rate (mg/hr- $\text{kg}^{0.7}$)
Rat	1.9	5.5	7.5	1.4	Not applicable
Mouse	3.7	7.5	39	5.2	Not applicable
Human (representative) ^c	3.4	55	Not applicable	1.4 ^d	75
Human (minimum)	2.4	39	Not applicable	1.4 ^d	54
Human (maximum)	8.7	141	Not applicable	1.4 ^d	192

^aPoet et al. (2005, 2006)

^bLowest tested dose

^cAverage of three similar individual values (Poet et al., 2006)

^dAssumed equal to rat ratio

The K_m value derived for the rat *in vitro* (2,510 mg/L) differs substantially from the K_m estimated from the *in vivo* data (21 mg/L). This difference may be related to unexpected difficulty with measuring 1,4-dioxane metabolism *in vitro* (i.e., the inability to detect 1,4-dioxane disappearance or HEAA appearance using microsomes). Human *in vivo* K_m s were estimated by multiplying the *in vitro* values by the *in vivo/in vitro* ratio for the rat. K_m s for representative, minimum, and maximum cases were 32, 29, and 147 mg/L.

Estimation of K_{me} for the Rat

The first order rate constant for the urinary elimination of the 1,4-dioxane metabolite HEAA by rats was estimated based on fit to the time course for total amount of HEAA eliminated in urine by rats dosed with 1,4-dioxane by iv (10 or 1,000 mg/kg) or gavage administration (10, 100, or 1,000 mg/kg) (Young et al., 1978). Dose-specific $V_{max}C_s$ (derived as described above) were used. The oral absorption rate constant for the rat was assumed to be equal to the best-fit value derived for the mouse ($K_A = 0.8$). The optimized value of K_{me} for the rat was $0.48 \pm 0.049/\text{hr}$ (93.0 % of variation explained). The model fit to the rat urinary metabolite data is shown in **Figure 4**.

Kme values were also estimated for each of data set individually. The optimal Kme values \pm the standard deviations generally encompassed the optimal values for all five data sets considered together. The single exception was the low dose (10 mg/kg) iv data, where an optimal fit was found with $K_{me} = 0.16 \pm 0.02/\text{hr}$. Because the optimal Kme for an equal oral dose was more in line with the group Kme value ($0.62 \pm 0.11/\text{hr}$), a dose-dependence in Kme did not seem to be indicated. The Kme value derived for the rat using all five data sets was used in the modeling.

Estimation of Kme and VDMC for the Mouse.

The volume of distribution of the 1,4-dioxane metabolite HEAA (VDMC) and the rate constant for urinary elimination of HEAA were optimized based on the fit to the time course of HEAA in blood of mice dosed with 200 or 2,000 mg/kg 1,4-dioxane by gavage (Thrall et al., 2005). The resulting values were $VDMC = 0.83 \pm 0.12 \text{ L/kg}$ and $K_{me} = 0.35 \pm 0.02/\text{hr}$ (56.7 % of variation explained). If the low-dose HEAA data were included, a similar Kme value resulted (0.40/hr), but VDMC was significantly reduced (0.56 L/kg), and the fit deteriorated substantially (41.7% of variation explained). The VDMC and Kme values from the mid- and high-doses (with the low dose omitted) were used in modeling (**Figure 3**).

Model Validation/Fit to Other Rodent Data

Model outputs were compared to other data not used in fitting model parameters. The model predictions gave an excellent match to the 1,4-dioxane exhalation data after a 1,000 mg/kg iv dose. 1,4-Dioxane exhalation was overpredicted by a factor of ~ 3 for 10 mg/kg iv dose. Similarly, the simulations of exhaled 1,4-dioxane after oral dosing were excellent at 1000 mg/kg, very good at 100 mg/kg (within 50%), but poor at 10 mg/kg (model overpredicts by a factor of five). The prediction of the 1,4-dioxane exhalation data (Young et al., 1978) is shown in **Figure 5**.

The simulation of blood 1,4-dioxane concentrations in rats exposed to 50 ppm 1,4-dioxane (Young et al., 1978) was excellent (**Figure 6**), but total excretion in urine was under predicted by a factor of 3 (data not shown). In order to match the model prediction to the data for HEAA excretion, the inhalation rate had to be increased by factor of almost 4, and blood concentrations were no longer accurately predicted. While restraint in a head-only chamber (Young et al., 1978) might be expected to cause some stress, a four fold increase in ventilation rate seems unlikely.

Predictions of blood concentrations of 1,4-dioxane and HEAA were made for mice exposed to a low dose (20 mg/kg) of 1,4-dioxane by gavage (Thrall et al., 2005). Predictions were consistent with the measured levels of 1,4-dioxane in blood not being distinguishable from the background of the method ($\sim 1.6 \text{ mg/L}$). The model dramatically underpredicted the blood concentrations of HEAA 0.5 and 1 hr after dosing, while overpredicting at 2 hrs (**Figure 7**). The model predicted that HEAA levels would be above the background of the method ($\sim 1.1 \text{ mg/L}$) at the 3 and 6 hr sample points, but they were not.

Fit of the Model to Human Volunteer Data

The fit of the model to the human data (Young et al., 1977) (**Figures 8 and 9**) was problematic. Using physiological parameters of Brown et al. (1997) and measured partitioning parameters (Thrall et al., 2005; Reitz et al., 1990) with no metabolism, measured blood 1,4-dioxane concentrations reported by Young et al. could not be achieved unless the estimated exposure concentration was increased from 53 to 100 ppm. Inclusion of any metabolism necessarily decreased predicted blood concentrations. If estimated metabolism rates were used (**Table 1 and 2**) with the reported exposure concentration, urinary metabolite excretion was underpredicted. Urinary metabolite excretion rates could be matched if either exposure concentration was increased to 62 ppm, or alveolar ventilation (QPC) was increased to 17 L/hr-kg^{0.74}. Both of these adjustments are plausible. Because the volunteers were given “bottled water, coffee, and a sandwich on demand” (Young et al., 1977) it is possible that additional 1,4-dioxane partitioned into food and beverages, increasing the total dose. The QPC estimate taken from Brown et al. (1997) (QPC assumed equal to cardiac output), 13 L/hr-kg^{0.74} is on the low side; the average value reported by Price et al. (2003) is 18 L/hr-kg^{0.74}. The ventilation rate used by Reitz et al. (1990) equates to a QPC of 30 L/hr-kg^{0.74}, which seems inconsistent with the low activity levels (volunteers were seated in an exposure chamber, Young et al., 1977). With the ventilation rate or concentration adjusted to match urinary excretion, the human model predicts significantly lower blood concentrations of 1,4-dioxane (~6 fold) than reported by Young et al. (1977). Conversely, if the estimated exposure concentration is increased by a factor of ~6, model predictions are consistent with measured blood 1,4-dioxane concentrations of individuals P, T, and G, but urinary excretion of HEAA is overestimated by a factor of ~6.

To increase the predicted level of 1,4-dioxane in human blood, both Reitz et al. (1990) and Leung and Paustenbach (1990) decreased the effective volume of distribution for the parent compound. The effective volume of distribution is the sum of the blood volume and the sum of the tissue volume multiplied by the ratio of the tissue:air and blood:air partition coefficient for all the tissues. Reitz et al. (1990) decreased the effective volume of distribution by doubling the blood:air partition coefficient, while Leung and Paustenbach (1990) reduced the tissue:air partition coefficient of the largest compartment, the slowly perfused tissues, by a factor of 2.5. The validity of these adjustments need to be considered. The original human blood:air partition coefficient (Reitz et al., 1990; Leung and Paustenbach, 1990) was confirmed by Thrall et al. (2005). The measured rat muscle:air partition coefficient was 997 ± 254 (Leung and Paustenbach), but Reitz et al. (1990) used the liver:air partition coefficient (1557) in place of the measured muscle:air value. The measurements of Thrall et al. (2005) (PSA= 1348 for rat, 1705 for mouse) confirm that the originally measured value of the rat muscle:air partition coefficient was too low. Thus the manipulation of the slowly perfused tissue partitioning by Leung and Paustenbach does not seem justified. 1,4-Dioxane appears to be rapidly distributed into tissues (brain, liver, kidney, and testes), with peak concentrations of radiolabel achieved within 15 minutes of ip injection (Mikheev et al., 1990). The tissue/blood ratios of radiolabel (Mikheev et al., 1990) were consistent with the PRA/PB ratio of 1,4-dioxane. Overall, the information on 1,4-dioxane partitioning does not

support the alterations Reitz et al. (1990) and Leung and Paustenbach (1990) made in their attempts to fit the human data of Young et al. (1977).

Fit of the Model to Human Occupational Exposure Data

In contrast to the fit to the volunteer blood concentrations, the fit to the urinary concentrations of 1,4-dioxane and HEAA in occupationally exposed workers (Young et al., 1976), the fit was excellent (**Table 3**). Because there is no “urine compartment” per se, some assumptions were made to convert the Young et al. (1976) urinary concentration data into estimated body burden. It was assumed the urinary concentration \times urine production rate = body burden \times elimination rate into urine. The urine production rate was assumed to be 1 ml/min (Young et al., 1977). The elimination rate of 1,4-dioxane into urine by humans (0.0033/hr) was taken from Young et al. (1977). The elimination rate of HEAA into urine was the value derived from the mouse model (0.35/hr). The group average values of estimated body burden of 1,4-dioxane and HEAA are within 10% of the modeled group average value.

Table 3. Comparison of Model Predictions and Experimental Data for Concentrations of 1,4-Dioxane and HEAA in Urine of Workers

Employee (Body Weight, kg; workdays)	1,4-Dioxane in air (ppm) ^a	Estimated 1,4-dioxane in body (mg)		Estimated HEAA in body (1,4-dioxane mg equivalent) ^a	
		Estimated ^a (mean \pm SD)	Model prediction	Estimated ^a (mean \pm SD)	Model prediction
A (74.8, 1)	1	6.88	3.42	0.91	3.49
B (110.7, 5)	1.6 \pm 0.5	5.28 \pm 3.2	8.04	3.47 \pm 1.46	7.22
C (74.4, 4)	2.0 \pm 1.0	5.76 \pm 0.64	6.81	9.38 \pm 2.32	6.95
D (79.4, 5)	1.8 \pm 0.4	5.92 \pm 2.24	6.54	7.09 \pm 3.45	6.53
E (78.5, 5)	1.1 \pm 0.6	4.80 \pm 1.12	3.95	6.73 \pm 2.14	3.96
Average (83.56, 4)	1.6 \pm 0.7	5.60 \pm 1.92	6.11	6.25 \pm 3.26	6.0

^aBody burden after 7.5 hrs exposure, based Young et al. (1976), estimated as described in text

DISCUSSION

Comparison with Previous PBPK Models

The partition coefficients used in this work (Thrall et al., 2005), have previously been compared to those used in previous PBPK models. Perhaps the most important comparison is that the results of Thrall et al. (2005) confirm the measured human blood:air partition coefficient values reported by Reitz et al. (1990), but not used in the modeling in that paper.

The VmaxC, Km, and Kme derivations for the rat for this modeling effort and the previous efforts (Reitz et al., 1990; Leung and Paustenbach, 1990) drew on the same experimental data sets (Young et al., 1978). The rat VmaxCs derived in this effort (7.5 and 12.7 mg/hr·kg^{0.7}, for uninduced and induced rats, respectively) were intermediate between the values determined by Leung and Paustenbach (1990) (normalized values of 5.0 and 9.2 mg/hr·kg^{0.7} calculated from reported Vmax values) and Reitz et al. (1990) (13.7 mg/hr·kg^{0.7}) and were similar to the value derived from scaling the *in vitro* data (Poet et al., 2005). The ratio of induced VmaxC to uninduced VmaxC determined by Leung and Paustenbach (1990) was similar to the ratio from the current effort (current: 1.7, previous: 1.8). The *in vivo* rat Km for the current effort (21 mg/L) was intermediate between the Reitz et al. (1990) and Leung and Paustenbach (1990) values of 7.5 and 29.4 mg/L, respectively. The VmaxC/Km ratios for the current effort (0.36 and 0.60 L/hr·kg^{0.7}, uninduced and induced) were closer to the VmaxC/Km ratio of Reitz et al. (1990) (0.47 L/hr·kg^{0.7}) than Leung and Paustenbach (0.67 and 0.12 L/hr·kg^{0.7}, uninduced and induced). The Kme value of 0.28/hr used by Reitz et al. (1990) appeared to have been derived only from the iv data. In contrast, the current evaluation (Kme = 0.48/hr) used both iv and oral data, and one of the iv data sets was found to best fit a much lower Kme than the other data sets, as discussed above.

Reitz et al. (1990) estimated VmaxC and Km values for mice by averaging the values derived for rat and humans, but had no data against which to validate these parameters. In the current effort, *in vitro* data indicated that the mouse Km was similar to the rat value (Poet et al., 2005). The *in vivo* rat Km was identified as ~21 mg/L by optimization. This value is similar to the value of 16.2 mg/L previously estimated by Reitz et al. (1990). The VmaxC estimated by Reitz et al. (10 mg/hr·kg^{0.7}) is significantly lower than the value estimated using fits to the 200 and 2000 mg/kg dosing data (39 and 45 mg/hr·kg^{0.7}, respectively). It is possible that the VmaxC identified for 200 mg/kg does not represent an “uninduced” value, but rather a value that is not induced to the same extent as the 2000 mg/kg dose. In rats, the transition from doses that do not induce 1,4-dioxane metabolism to doses that do induce metabolism is between 100 and 300 mg/kg. The larger discrepancy in mice, as compared to rats, between the *in vivo* best-fit value and scaled *in vitro* VmaxC also supports the theory that the 200 mg/kg dose induced 1,4-dioxane metabolism.

Fit of the Model to Rat and Mouse Experimental Data

The optimized model parameters provide a good fit to the blood measurements of 1,4-dioxane in mice and rats (**Figure 2, 3, and 6**) and exhaled breath 1,4-dioxane at mid- to high-doses (**Figure 5**). The poorer fit to the low-dose exhaled breath 1,4-dioxane may reflect limited metabolism in the upper respiratory tract which does not contribute significantly to whole body metabolism, but scrubs some 1,4-dioxane from exhaled breath. The fit to and prediction of the HEAA data was somewhat less successful than the prediction of the 1,4-dioxane data. The lack of fit to some of the HEAA data is likely due to an overly simplistic description of its distribution and elimination (single compartment, first order elimination).

Application of the Human Model in Risk Assessment

Clearly there is sufficient data to support the use of a PBPK model rather than generic scaling factors for interspecies scaling of dosimetry. Since there is limited human data on which to validate the model, the most appropriate use of the model needs to address uncertainties associated with the limited *in vivo* data and the uncertainties in the *in vitro* data (*i.e.*, discrepancies between rat *in vitro* and *in vivo* Kms). An issue that deserves consideration is that the unadjusted human model predicts significantly lower blood concentrations of 1,4-dioxane (~6 fold). If blood or tissue 1,4-dioxane level were to be used as a dose metric in risk assessment, the unadjusted model would result in a less conservative assessment. We can see three options that might be pursued: (1) manipulate the human model parameters to match the available human *in vivo* data, (2) use the unadjusted human model as-is, or (3) use the unadjusted human model, but multiply 1,4-dioxane dose metrics by the 6-fold discrepancy with the available experimental data. The first and third options assume that the Young et al. (1977) human data are “right”, and the model predictions are adjusted, while under the second option, the model is “right” and the data are “wrong”. We recommend option (3) as the impact of this discrepancy is clearly and consistently accounted for in the risk assessment. Under option (1), the parameter adjustments that are made could have a different impact under low-dose or route-to-route extrapolation that would be complicated to identify. We cannot recommend option (2) in isolation because of the potential skewing of the risk assessment towards inadequate health protection, but it may be worthwhile to use option (2) in combination with option (1) or (3) as a possible lower-bound estimate. Despite the limitations of the human model, the use of a validated mouse model and a refined rat model, combined with a better understanding of the validity of the human model provide the tools for more scientifically credible risk assessments than could be done in the absence of these models, or the previously available PBPK models for 1,4-dioxane.

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Appendix A

Personal communication from Dr. Bill Stott, Dow Chemical Company, Midland, Michigan

1059 - 14

Dioxane: Human Inhalation Study 9.22.76

WORK SHEET

Purpose: assay for 1,4-Dioxane in plasma
and urine of inhalation exposed humans

method: see publication Braun (1976)

results:

Plasma (ppm) Dioxane

subjects →

Time ↓	P	T	C	G	avg
1 0.5 hrs	1.5 2.5 4.5 4.5	0.3 0.3 1.7 2.5	1.7 1.7 5.7 8.9	0.5 0.5 3.7 2.5	1.0
2 1.0 hrs	4.6 4.6 9.0 7.4	2.1 2.1 8.7 6.9	5.5 5.5 14.5 13.5	3.6 3.6 4.7 8.0	4.4
3 2.0 hrs	8.7 8.7 9.5 9.4	6.9 6.9 8.7 10.7	14.1 14.1 16.5 14.6	4.7 8.0 4.7 10.6	9.4
4 3.0 hrs	9.5 9.5 13.9 10.5	9.2 9.2 12.8 9.3	17.2 17.2 21.6 18.4	4.7 10.6 10.9 12.8	10.6
5 4.0 hrs	10.7 10.7 10.1 10.0	9.3 9.3 12.0 9.2	20.5 20.5 19.7 22.1	11.9 11.9 12.5 12.1	13.1
6 5.0 hrs	10.1 10.1 (25) 3.5	11.6 11.6 (28) 14.1	19.6 19.6 (15.8) 22.2	12.3 12.3 (46) 12.2	13.4
7 6.0 hrs	9.0 9.0 10.1 10.0	10.1 10.1 10.1 10.0	20.7 20.7 10.1 10.0	12.2 12.2 6.9 6.2	13.0
8 1.0 hr	5.2 5.2 19. 2.3	7.7 7.7 2.3 1.5	10.1 10.1 5.2 4.7	6.9 6.9 3.3 3.1	5.0
9 2.0 hr	2.1 2.1 0.9 0.7	1.9 1.9 0.5 1.7	5.2 5.2 0.7 2.1	3.2 3.2 1.5 1.3	2.1
10 3.0 hr	0.8 0.8 0.1 0.9	1.1 1.1 0.2 0.7	1.9 1.9 0.6 1.9	1.5 1.5 0.7 0.7	1.4
11 4.0 hr	0.5 0.5 (0.6) 0.1	0.4 0.4 (0.1) 0.1	1.2 1.2 (0.1) 0.1	0.7 0.7 (0.4) 0.1	0.7
12 5.0 hr	0.3 0.3 (0.6) 0.1	0.1 0.1 (0.1) 0.1	0.5 0.5 (0.1) 0.1	0.2 0.2 (0.1) 0.1	0.3
13 6.0 hr	<0.1	<0.1	0.2 0.1	<0.1	

50 ppm

READ BY _____ DATE _____

1059 - 14

Urine (ppm) Dioxane 9-28

WORK SHEET

#	Time	P	T	C	G	A
1	0-6	3.7 2.2 3.1	3.0 3.5 5.2	2.0 2.4 3.2	2.7 1.7 2.2	3.0
2	6-8	3.5 1.03 0.77	0.91 0.57 0.71	0.53 0.35 0.79	0.27 0.25 0.66	0.5
3	8-10	0.6 0.01 0.23 0.01	0.19 0.35 0.27	0.24 0.12 0.18	0.23 0.22 0.22	0.6
4	10-12	0.02 ⁺	0.03 ⁺	0.10 ⁺	0.03 ⁺	0.5
5	12-14	nil	nil	nil	nil	
6	14-16	nil	nil	nil	nil	
7	16-24	nil	nil	nil	nil	

+ S/N = 15

Urine (ppm) HEPA

Sample	P	T	C	G	average	average
interval	vol. conc.	vol. conc.	vol. conc.	vol. conc.	conc.	avg. V
0-6	(1201) 303 128	(405) 487 114	(242) 273 109	(170) 300 121		
6-8	(597) 214 83	(138) 509 82	(130) 585 122	(630) 193 128		
8-10	(174) 477 48	(222) 674 48	(200) 491 28	(314) 321 31		
10-12	(107) 436 39	(230) 218 26	(17) 277 16	(100) 475 53		
12-14	(280) 138 18	(107) 341 15	(12) 224 10	(400) 132 50		
14-16	(312) 51 6.7	(14) 95 1.8	(200) 15	(674) 60 6.7		
16-24	(310) 5.8	(403) 4.5	(243) nil	(378) 8		
24-36	nil	nil	nil	nil		
36-48	nil	nil	nil	nil		
Total mg of HEPA	690mg	522mg	570mg	791mg		

mg
(ml) mg/ml

READ BY _____ DATE _____

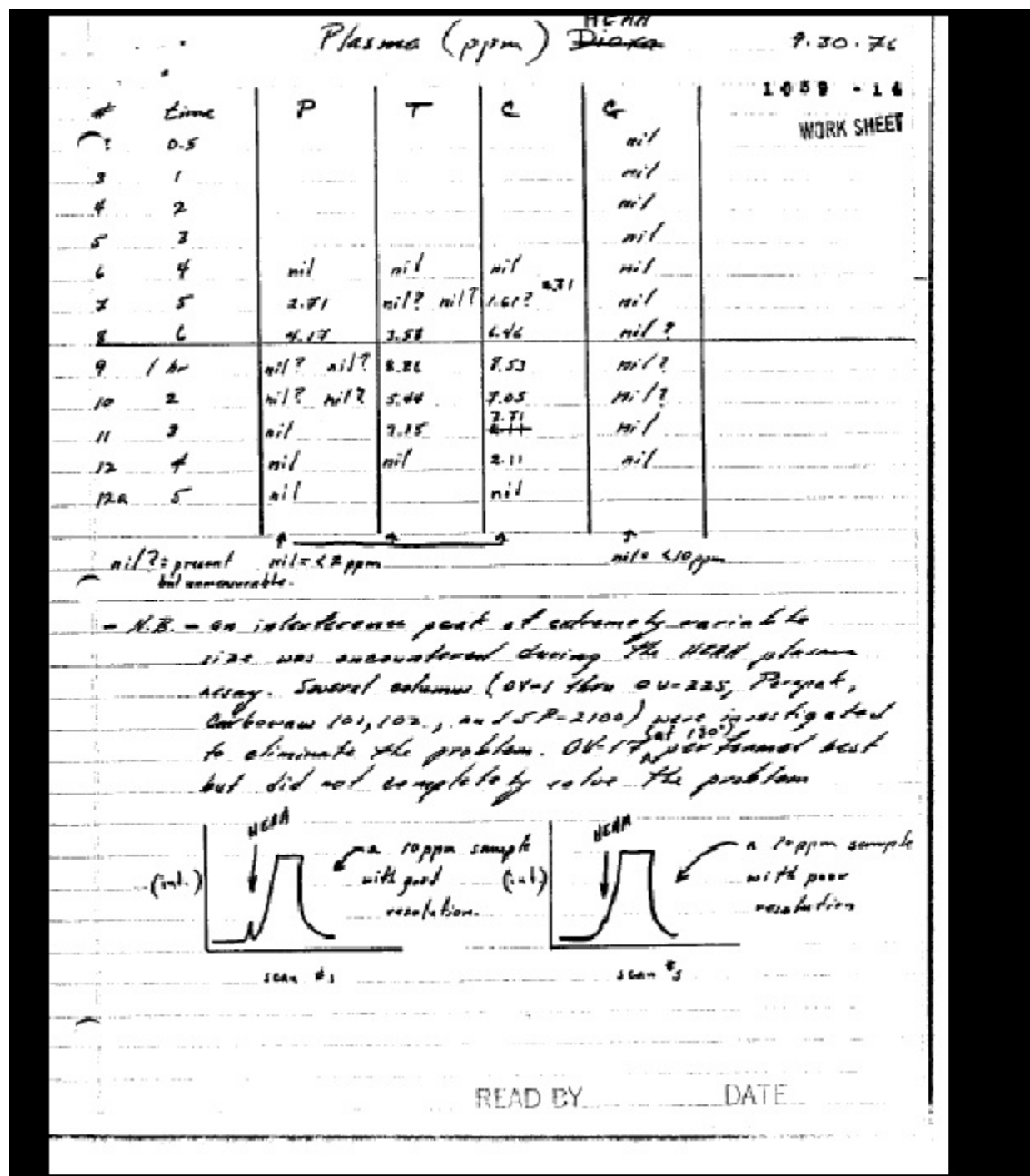


Figure 1. Structure of 1,4-Dioxane PBPK Model

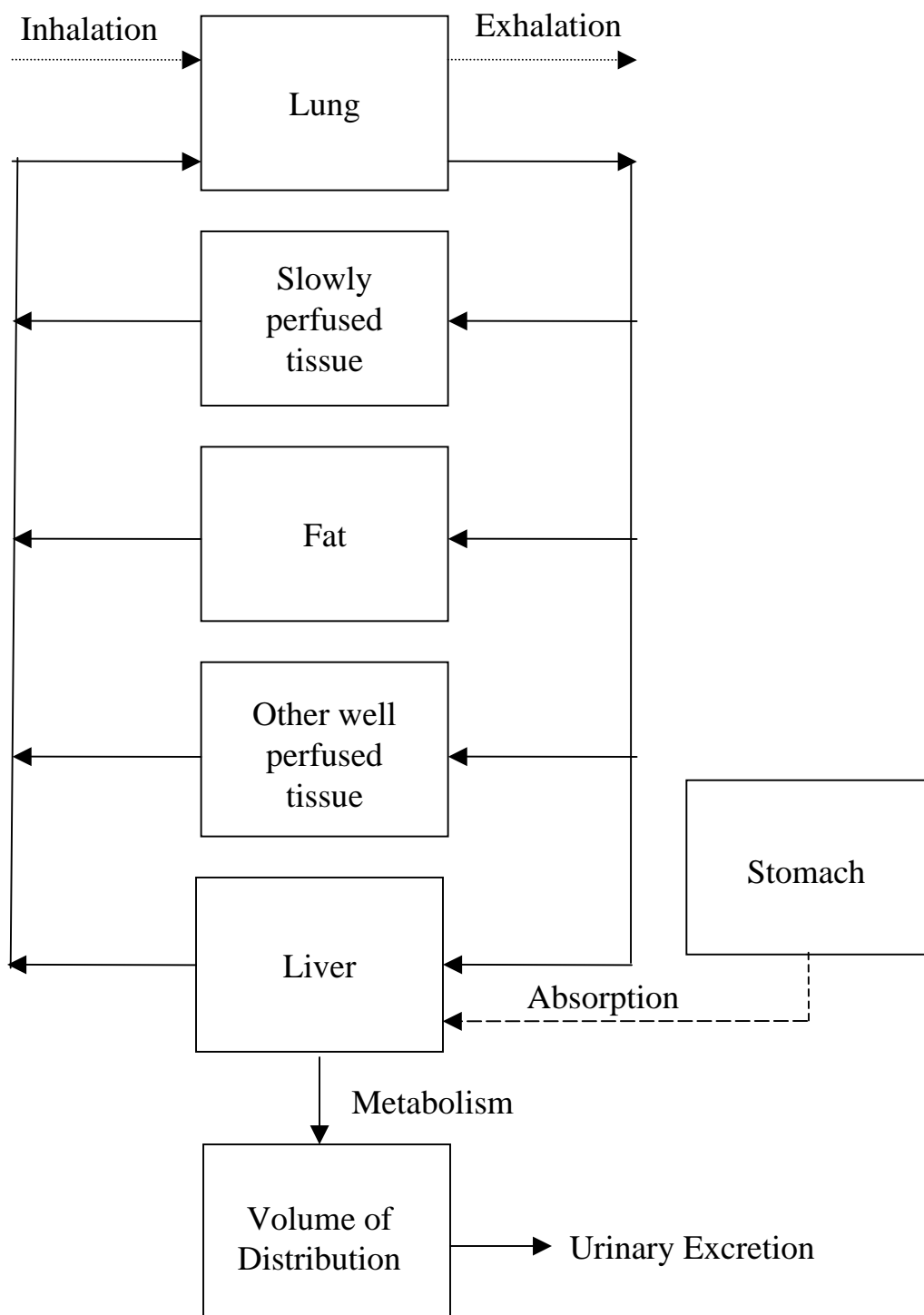


Figure 2. Fit to rat iv data (Young et al., 1978)

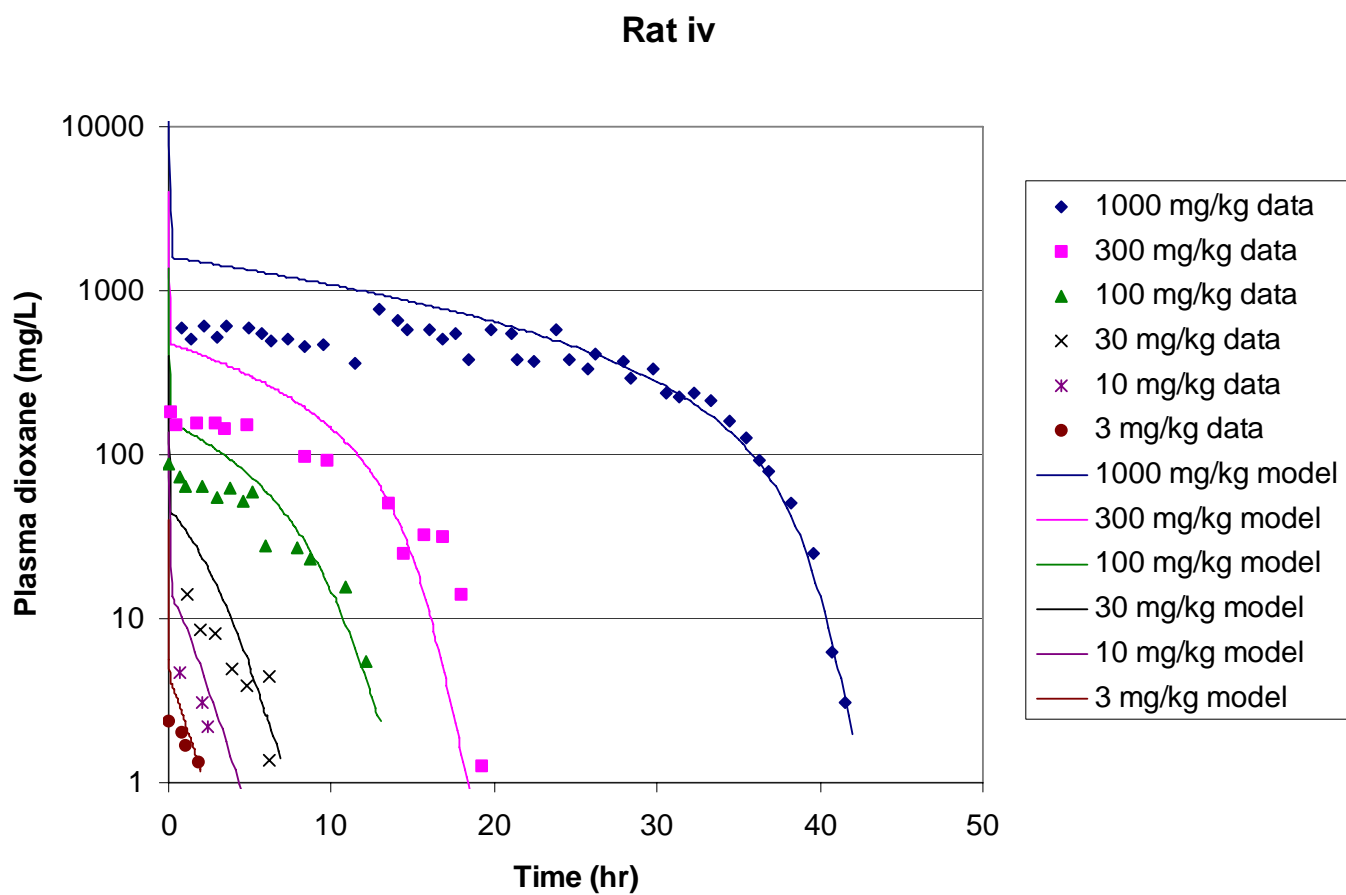


Figure 3. Fit to mouse gavage data (Thrall et al., 2005)

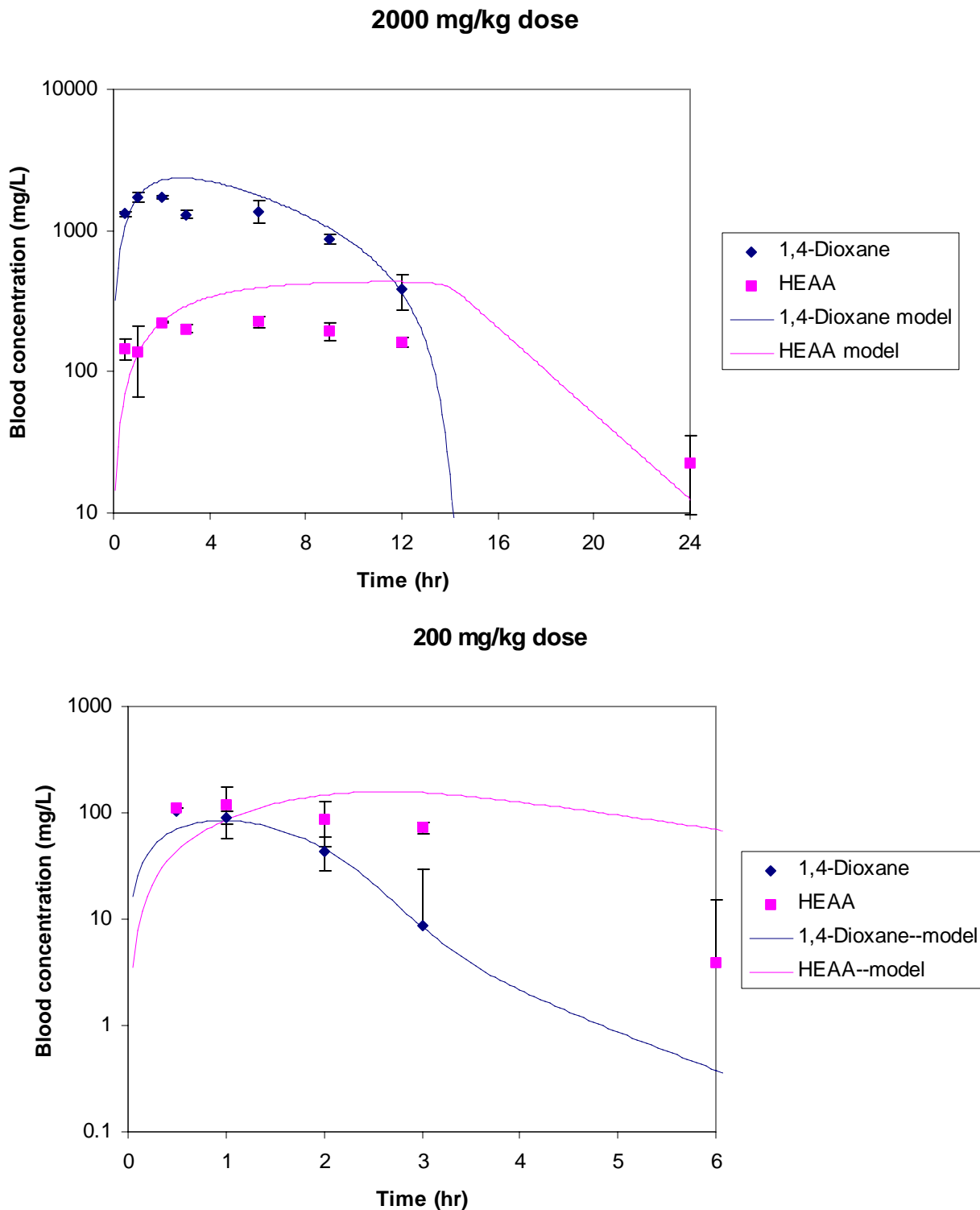
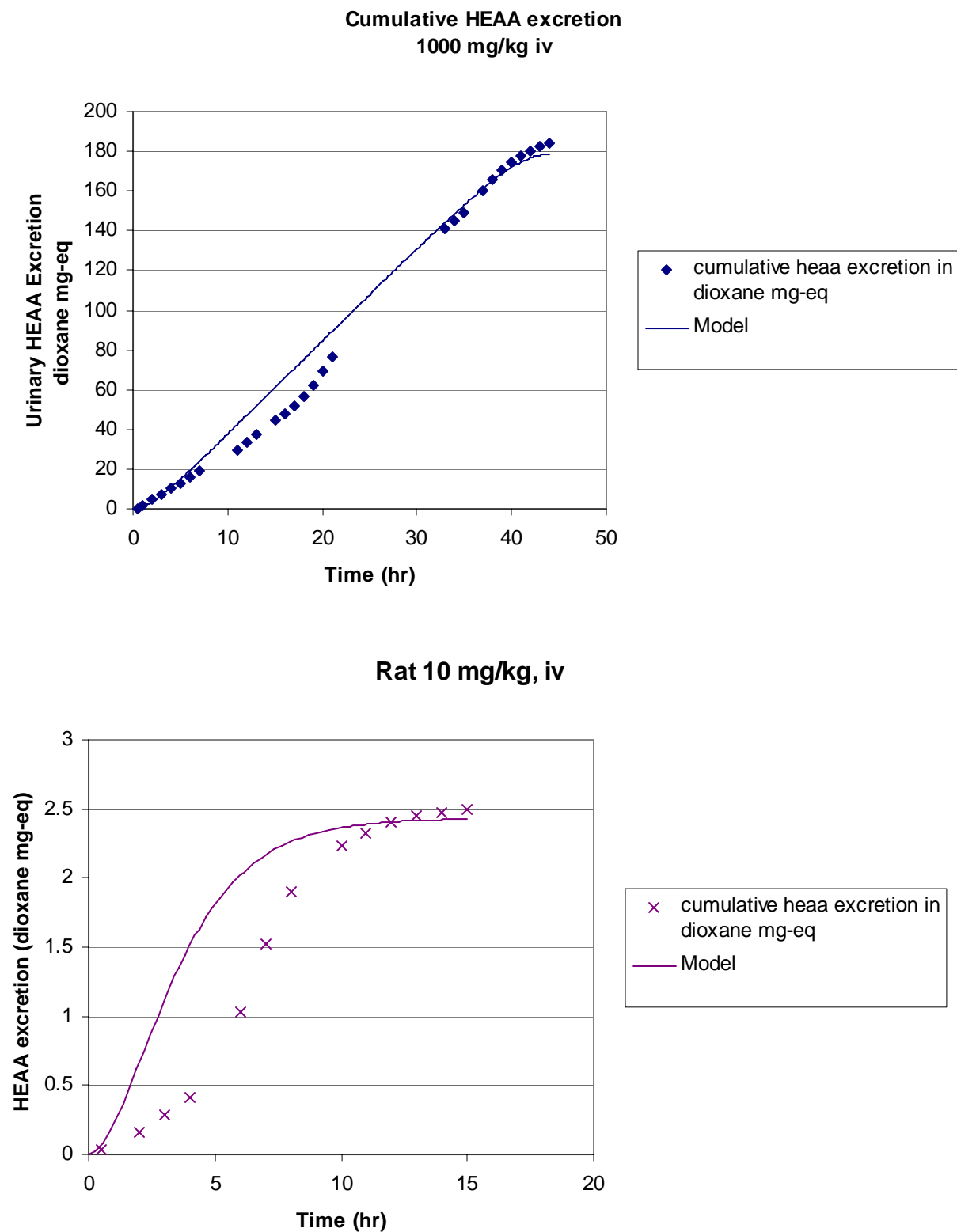


Figure 4. Fit to rat urinary excretion data



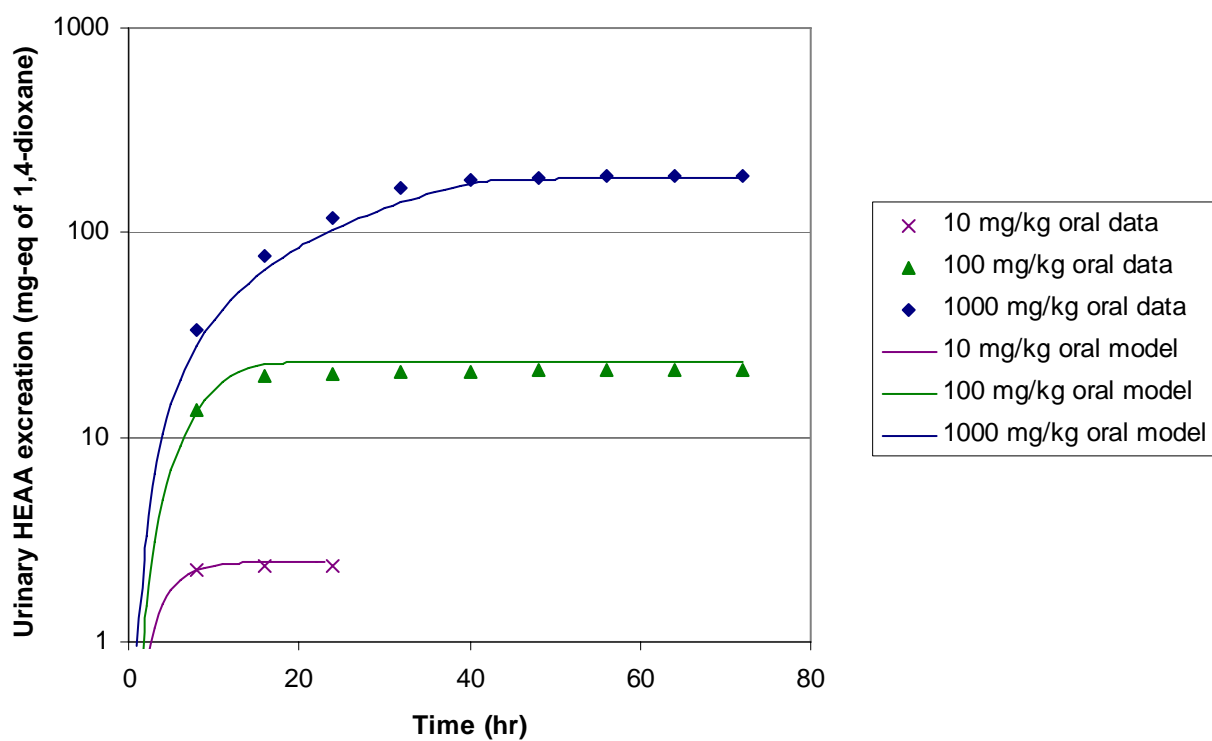
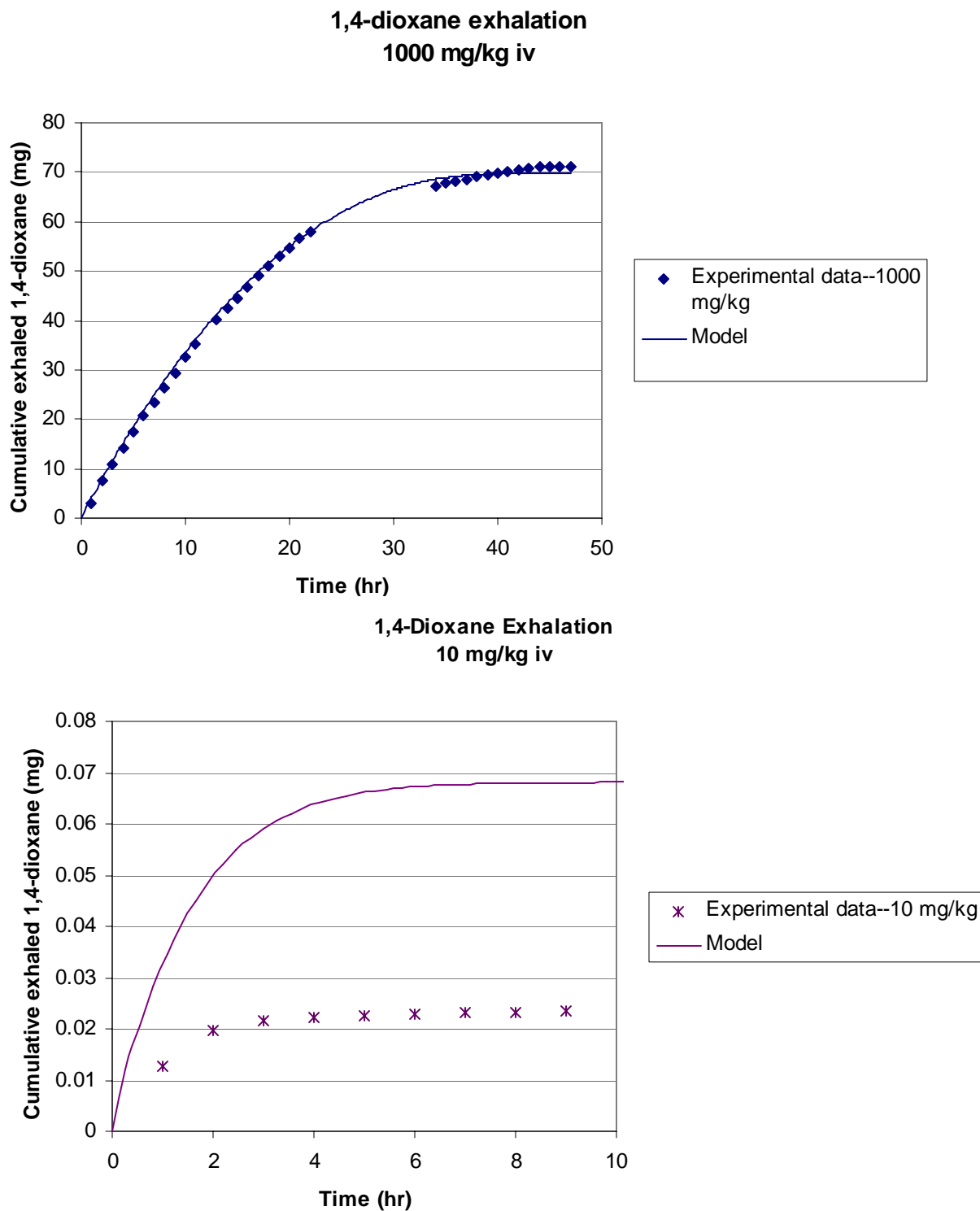


Figure 5. Prediction of 1,4-dioxane exhalation by rats



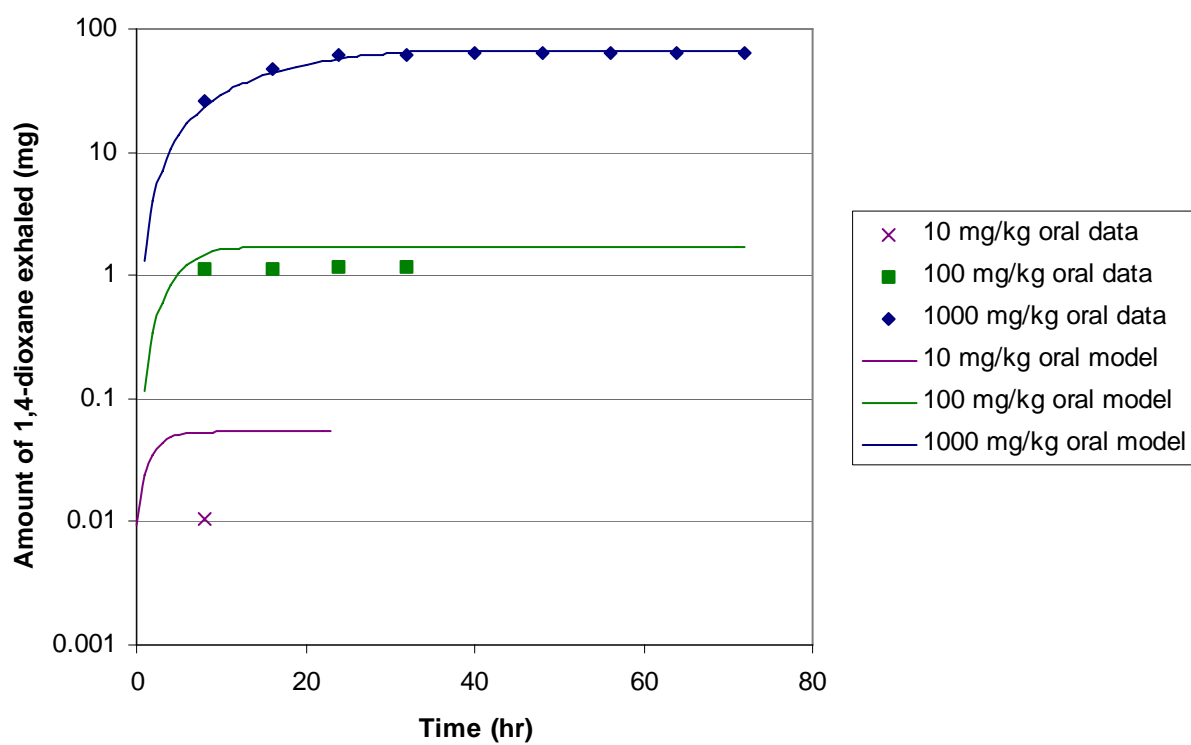


Figure 6. Prediction of 1,4-dioxane in blood of rats
exposed by inhalation

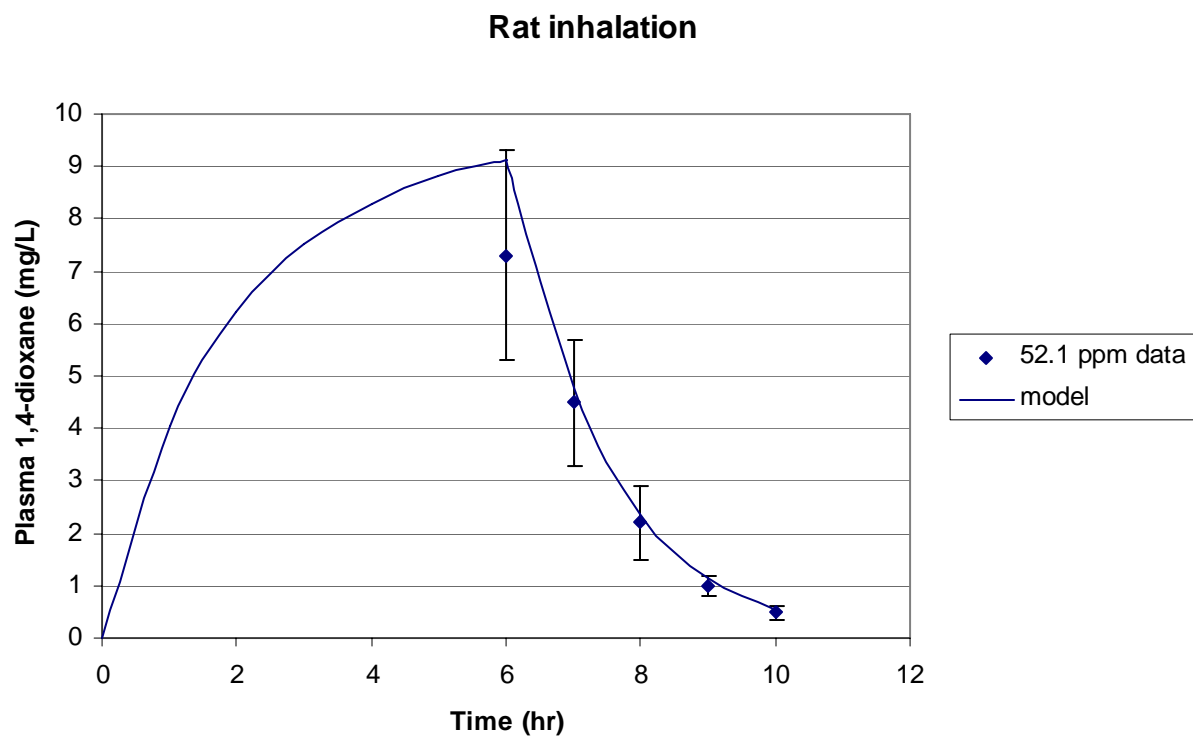


Figure 7. Prediction of mouse low-dose

20 mg/kg dose

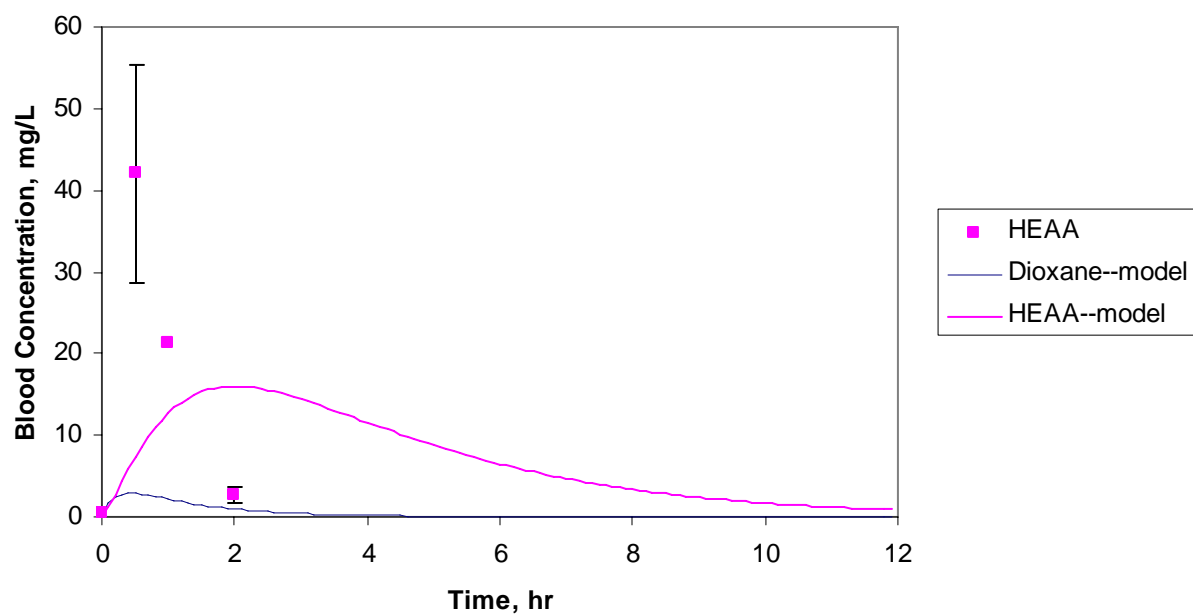


Figure 8. Prediction of human volunteer data (1,4-Dioxane) (Young et al., 1977)

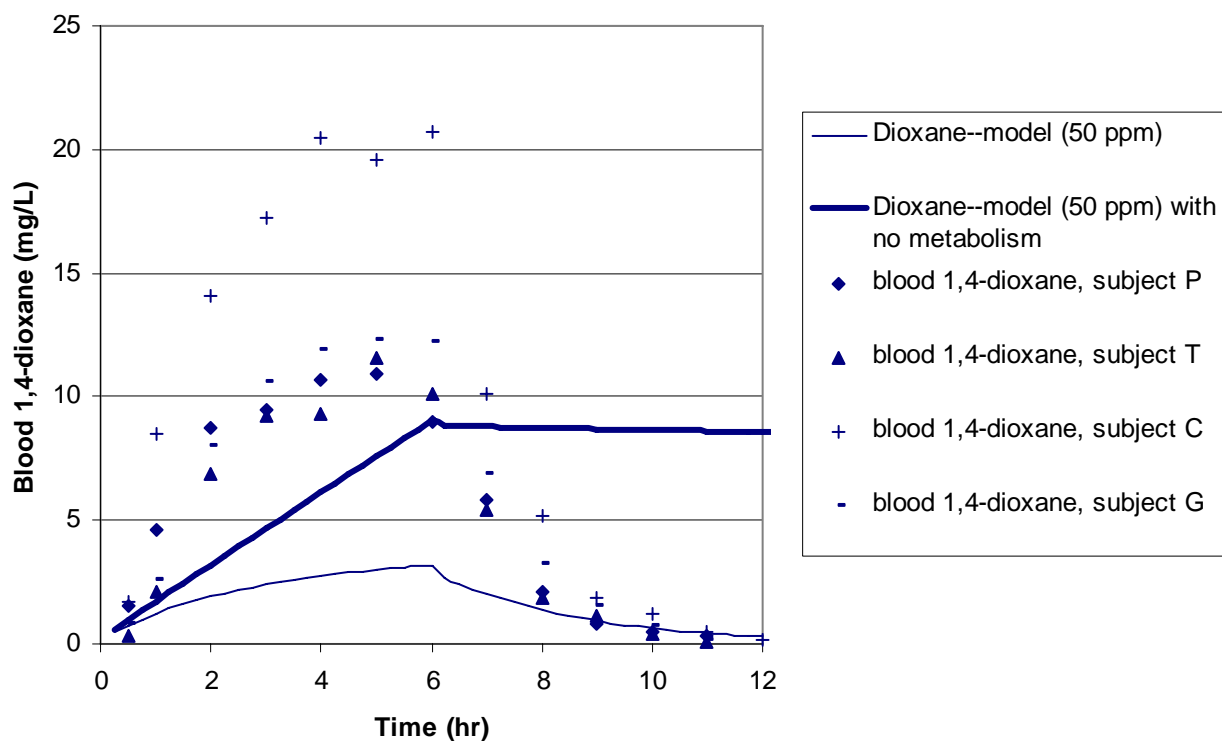


Figure 9. Prediction of human volunteer data (HEAA) (Young et al., 1977)

